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National Foundation Conference on Congenital Malformations

INTRODUCTION TO THE NATIONAL FOUNDATION CONFERENCE ON CONGENITAL MALFORMATIONS

THE following papers were presented at a conference held on April 5, 1959, under the auspices of The National Foundation (originally The National Foundation for Infantile Paralysis).

In the summer of 1958, The National Foundation, which for more than 20 years had supported extensive research in the field of poliomyelitis, announced that it was broadening its program to include congenital malformations and arthritis. Accordingly, two conferences were held, one on rheumatoid arthritis and one on congenital malformations, in order that The National Foundation's medical advisory committees might hear a review of what has already been accomplished in these fields and what needs to be done. The papers on rheumatoid arthritis will appear in a subsequent number of the JOURNAL.

The road to prevention of congenital malformations and to the proper care of those afflicted by them seems long and difficult. But those attending the conference, who had participated in the program of The National Foundation during its early days, recall vividly how difficult or impossible the road to be traveled at that time appeared.

The first paper presented traces man's experience with congenital malformations from the edge of history, through folklore, to the better but still imperfect understanding of the present day. In addition to the historical discussion, papers dealing with the causes of malformations, their experimental production, the surgical treatment as exemplified by the handling of congenital malformations of the central nervous system, and, finally, a summary with suggestions for future investigations were presented. I wish to express the appreciation of The National Foundation to those who participated in the conference. From their comments it is very obvious that here is a field which calls for a great deal of attention.

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CONGENITAL MALFORMATIONS IN THE PAST

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TO DISCUSS the past at a conference designed to consider the future of teratology may seem a superfluous task. Yet the uses of the past are clearly demonstrable in the field of teratology, a science that can be traced to the earliest times of human history. From time immemorial, men and women of all continents and countries have been fascinated by monstrous human beings and animals. In fact, they recorded such curiosities before they learned the arts of reading and writing. This is demonstrated in artistic expressions of very primitive peoples. For instance, a rock drawing found in New South Wales, Australia, shows a double-headed human male figure, 9 feet, 6 inches long, with six fingers on the right hand and four on the left, the remarkable work of an Australian aborigine who felt impelled to put on record an unusual human birth. A beautiful carving of chalk from New Ireland in the South Pacific represents a double-headed human figure with two, or probably, three arms, a case of dicephalus dibrachius well known to modern science. A wooden carving from the Solomon Islands suggests conjoined twins of the pygopagus type with union of the bodies and heads and the extremities shortened by achondroplasia (chondrodystrophy), a systemic skeletal malformation. This anomaly, though known to man for millenia, did not become a scientific entity until 1878 when Parrot[17] recognized it as a disorder of cartilage formation and called it "achondroplasia."

The remarkable expressions of primitive Australian man were published in 1943 by Brodsky[4] of Sydney, Australia, who collected many examples of art and legends demonstrating a knowledge of monstrosities and malformations in the native population of Australia and her surrounding islands. The teratologic knowledge of man living in a Stone Age civilization is expressed in such works of art which show remarkable power of detailed observation and description.

Written records of congenital malformations have come down to us from the ancient inhabitants of Babylonia. Such records were found in the form of clay tablets covered with cuneiform characters in a mound near the Tigris River

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in the nineteenth century. The tablets belonged to the Royal Library of Nineveh which was assembled under the Assyrian King, Asshurbanipal, who lived in the seventh century B.C. It is thought, however, that these records date back to 2,000 B.C. and that the observations on which they are based were much older than this.[3]

The Chaldeans are known as the founders of astrology, the science of divination, the science of foretelling the future from the constellations of the stars, the sun, and the moon. The future was predictable not only from the course of the heavenly bodies, but also from terrestrial events. The flights of birds, the organs of sacrificial animals, and the births of deformed children were included in the calculations which predicted events to come. The abnormalities of newborn children were considered a reflection of stellar constellations and could be used, therefore, to foretell the future with as much accuracy as the stars themselves.

VOL.
10
1959

Among the many astrologic and astronomic tablets found in the library of Nineveh there were two which contain a list of sixty-two human malformations with the prophetic meanings attached to them by the Chaldean diviners.

Only a few of the forecasts listed by Ballantyne can be given as examples:

When a woman gives birth to an infant
that has the ears of a lion, there will be a powerful king in the country;
that wants the right ear, the days of the master (king) will be prolonged (reach old age);
that wants both ears, there will be mourning in the country, and the country will be lessened (diminished) . . . .

Eleven malformations of the ear are enumerated and their prognostic value is specified. Other malformations are listed that may be of interest to the plastic surgeon:

When a woman gives birth to an infant
whose nostrils are absent, the country will be in affliction, and the house of the man will be ruined;
that has no lips, affliction will seize upon the land, and the house of the man will be destroyed;
that has no fingers, the town will have no births . . . .
that has six toes on each foot, the people of the world will be injured . . . .

The orthodontist may be interested in an infant
whose upper lip overrides the lower, the people of the world will rejoice . . . .

There are also statements of interest to the urologist and the endocrinologist:

When a woman gives birth to an infant
that has no well-marked sex, calamity and affliction will seize upon the land; the master of the house shall have no happiness;
that has no penis, the master of the house will be enriched by the harvest of his fields . . . .

Many types of twinning were known to these ancient writers such as the conjoined twins carved in wood by the aboriginal Australian:

> If a woman gives birth to
>
> twins joined back to back, the gods will abandon the country, the
>
> king and his son will abandon the city . . . .[12]

And so it goes through a long list of malformations and their meaning to the master of the house, the king, and the country. The remarkable thing about this catalogue is that, as Ballantyne[3] has pointed out, none of the recorded anomalies, with one exception, can be regarded as impossible or mythical. Most of the malformations enumerated are known to us today and are listed in modern publications on congenital malformations. Whatever we may think of the conclusions drawn by the Babylonian priests, we must admit that these founders of the science of teratology were excellent observers and recorders.

The people and the cities of Babylonia disappeared but Babylonian belief in divination has never died. Predictions from the birth of monsters and from other impressive events spread from Babylonia through neighboring lands, through Greece and Rome, and to other countries of Europe. Augury played an enormous role in Roman history, and Cicero[6] devoted two books to a discussion of divination in which he argued vigorously against this superstition while he let his brother, Quintus, present the arguments in its favor. From him we learn that the very word "monstra" had been chosen because of the monster's property of demonstrating the future. The stoic philosophers were the chief defenders of the belief that the future could be foretold through careful observation and interpretation of monsters and other portents. They considered those diviners as competent who "having learned the known by observation, sought the unknown by deduction." They believed in an orderly succession of causes, wherein cause was linked to cause. The birth of a hermaphrodite, for instance, was considered an ill omen by the early Romans.[19] Unfortunately they executed such bisexual children. They apparently thought that disaster could be prevented by removal of the monstrum, which, according to the Chaldeans, was merely an indicator, a symptom of the future misfortune. But the Romans mistook the symptom for the cause, an error not unknown to the teratologists of today.

During the Middle Ages the interpretation of monsters as portents continued and played an important role during the religious controversies of the Reformation. In 1523 Luther and Melanchthon jointly published a work under the title *Der Papstesel* interpreting the significance of a strange asslike monster which had been found floating in the Tiber. The monster was assigned from God, indicating the doom of the Papacy.[22] This prediction was balanced by the birth in 1569 of twins who were conjoined at the chest, with only one of the twins being baptized in time. The physician, Jacques Roy, who performed the autopsy, interpreted this event as intimating that the Catholic faith would survive that of the Huguenots.[13] Belief in the birth of deformed children as omens and portents can be followed through many popular pamphlets and broadsheets published for the entertainment of the public from the fifteenth to the eighteenth century.[9]

To us it is of interest that the Chaldean beliefs crossed the Atlantic and traveled into the New World with its European settlers. Although they seldom come to the surface, they are still transmitted in whispers and have not lost their grip on the human mind. In 1945 a candid autobiography of an American physician, Tryon,[21] appeared in which an account is given of the emotions and thoughts aroused in the author on the occasion of delivery of a monstrous child. The physician, who practiced in a Dutch community of Pennsylvania, was undecided at the time whether to get married or not, and he relates how his decision was influenced: "During this time I delivered a monstrosity and I suppose with all the other things I inherited from my distant German ancestry, was a strong streak of mysticism. The monster became a portent. . . . It was a sign, a portent that I could expect nothing good from the way things were drifting along." This physician's thoughts were probably not very different from those of other people of our time, but his candor and frankness are unusual and permit a glimpse into popular belief. It seems worthwhile to keep in mind that even in our day parents of a monstrous child may be plagued by antiquated views which must be discussed and corrected by an understanding physician.

VOL.
10
1959

While the Chaldeans made use of the birth of deformed children to predict the future, other theories are concerned with causation and explanation. These concepts, which represent the answer of the past to the questions of etiology, are less grandiose than those of the Chaldeans and limit their search to terrestrial events.

The belief that psychogenic factors play a role in the causation of congenital malformations is very widespread. This idea appears in many forms, but essentially two subgroups can be distinguished. One belief is that parental mental impressions at the time of conception or mental impressions of the mother during pregnancy influence the formation of the child by producing a kind of photographic effect upon the offspring. A different theory suggests that maternal frights, worries, shock, or stress can produce malformations in the child in a rather unspecific way so that the exciting factor has no direct relationship to the morphology of the defect.

Theories of mental impressions as a cause of malformations and monstrosities were thoroughly discussed by Ballantyne[2] who traces these beliefs from ancient times to the end of the nineteenth century.

The idea that mental impressions have a formative and molding effect upon the fetus apparently originated independently among people who were widely separated geographically as well as culturally. It existed not only among all the peoples of Europe, but also in the Near East, in India, China, Japan, and South America. It developed among the Eskimos and the African Negroes. It seems that this idea is inbuilt in the human brain and finds expression wherever children are observed who do not resemble their parents. This "photographic" theory was not used originally as an explanation of congenital anomalies, but was employed for eugenic purposes with the intention of changing and improving the fruit of man or animal. One of the best known examples is found in the Bible in the story of Jacob (Genesis, Chapter 30) who tried to obtain a large number of speckled offspring in Laban's flocks from which all the ring-streaked and spotted

animals had been removed. To this purpose Jacob peeled branches of various trees, thus producing white streaks on the rods which he placed in the watering troughs of the flocks. As the flocks conceived before the troughs, they brought forth ring-streaked, speckled, and spotted offspring. This method was applied chiefly to the stronger animals which went to Jacob, while the feeble, not exposed to the experiment, belonged to Laban. Needless to say, Jacob became exceedingly prosperous by this procedure.

Methods of mental "modification" were used in Greece where expectant mothers were encouraged to look at beautiful statues and pictures so that their children would be strong and beautiful. The method was considered effective by Empedocles[5] and by the Spartans whose law ordered pregnant women to look at statues of Castor and Pollux to make their children well formed and strong. The Romans continued the belief, and Pliny wrote that maternal and paternal thoughts at conception can shape the child.[2]

The idea of maternal impressions was also used in reverse to explain ill-formed children. For instance, the resemblance to monkeys of microcephalic or anencephalic children gave rise to the opinion that it is dangerous for women to look at monkeys during pregnancy. The birth of a black child to white parents was attributed to the picture of a Moor. It is most interesting to trace this concept through the centuries. The French surgeon, Ambroise Paré, considered a wayward maternal imagination as one of his thirteen causes of monsters. In his writings we see that this belief can be combined with scientific knowledge of embryology. Paré mentions that some people believed that after 42 days in the womb, the fetus is not endangered by the mother's imagination because once it has acquired a perfect figure, it cannot be altered by external impressions. Thus, already in the sixteenth century, it was believed by some that the organogenetic period of the embryo was passed after 6 weeks of gestation and that maternal impressions after that time cannot be accused of deforming the child, which shows that knowledge of embryologic time tables is compatible with superstitious beliefs. The best minds of the sixteenth century adopted the theory of maternal impressions, including the skeptic Montaigne[15] who, in an essay entitled "On the Power of Imagination," explained why this belief was so prevalent. Since man had observed that the mind had definite influence upon such organic functions as yawning, vomiting, potency, and impotence, many unexplained somatic disturbances were attributed to the mind. In the past as well as today psychosomatic influences are blamed for disorders without tangible causes. It was thought that the imagination works not only upon one's own body, but also upon that of others. In the days of Montaigne, transmission of contagious diseases was attributed to visual impressions. "And as an infected body communicates its maladies to those that approach or live near it, as we see in the plague, the smallpox and sore eyes, that run through whole families and cities . . . . so the imagination, being vehemently agitated, darts out infection capable of offending the foreign object." Thus, at a time when neither bacteria nor viruses were known as causative agents of contagious diseases, it was believed that communicable diseases could be transferred by visual exposure. Since imagination and fear could influence involuntary functions of the body, since

diseases could be transmitted by visual perception, it seemed very likely that maternal impressions could modify the growth of the developing fetus who is a part of the mother's body. Therefore, Montaigne states, "We know by experience that women impart the marks of their fancy to the bodies of the children they carry in their womb." These thoughts of an enlightened man of the sixteenth century explain why mental factors were and are used in the explanation of disorders for which no visible causes could or can be found. Similarly, we can and must expect that maternal impressions will be employed as explanations for malformations as long as we have no convincing explanations for the birth of defective children.

In the seventeenth and eighteenth centuries the theory of maternal impressions continued to flourish, and one finds the names of many outstanding scientists among its adherents. At the same time, the first voices were heard objecting to its validity and scientific foundation. It was pointed out that in consideration of the multiplicity of maternal impressions during the long 9 months of pregnancy, all children born should have marks and some should be spotted like leopards. It was observed that adverse maternal impressions were not always followed by the birth of defective children and that often abnormal children were born to mothers who did not have frightening experiences. Anatomy had progressed sufficiently to demonstrate that there were no nervous connections between mother and fetus. How could the mother's thoughts or fears be transmitted to her unborn child? It was known that the maternal and fetal circulations were separated. How could images be transmitted through the placenta?[2] During the nineteenth century the theory lost ground continually and German teratologists were particularly opposed to it. It was known then that most malformations are determined in the first weeks of gestation, while the tales of maternal impressions or frights usually referred to events late in pregnancy.

It should be mentioned as a curiosity that in the United States the theory survived throughout the nineteenth century and supporters could be found here among the leading medical authorities. In 1889 Keating's *Cyclopedia of the Diseases of Children*[10] still contained a special chapter on "Maternal Impressions" which is worth reading since it presents in clear and scientific language and by modern tabulation the most naïve credulity in maternal impressions. Ninety instances of defects in children were recorded together with "the cause or nature of the impression" and the "period of pregnancy" in which the impression occurred. Some of these cases are remarkable indeed. In one case the milkman whom the mother saw daily from the time of her marriage had one finger amputated, and the child born subsequently had only four fingers on one hand. In another case the mother lived next door to a man with a harelip and was apprehensive lest her child should be similarly deformed, and the child had a harelip. Another unfortunate mother was in her fourth month of pregnancy when she scuffled with a man who attempted undue liberties with her. The mother noticed that he had but one ear. When the child was born he had but one ear. These examples will suffice to show that the idea of maternal impressions held its own in its most primitive form in the medical literature of the nineteenth century. In our own times it has appeared in modern garb. Since fright can

cause a release of adrenal hormones and since cortisone can induce cleft palate in certain strains of mice, a new mechanism has been found for those who want to believe in the ancient theory. However, the evidence for this mechanism as a cause of human malformations is extremely meager to say the least, and it should be emphasized that those who did the experiments mentioned did not propose their application to the theory of mental stress.

In the past there may have been humanitarian reasons for the enlightened and progressive minds to support the theories of maternal impressions. Such theories were rather humane and harmless if compared with some other ancient explanations of birth defects.

There was a widespread belief that members of different species might be fertile with one another and thus produce monstrous offspring. This theory, which was termed the "hybridity theory" by Ballantyne,[2] probably originated in India and Egypt where the transmigration of souls from man to animal was taught, and animals were considered as equal or superior to human beings. A cross between different species was not considered repulsive and if a woman produced a monstrous child who resembled a particular animal, the child was paid the same respect due that animal in the official religion. For instance, at Hermopolis in Egypt the mummy of a human anencephalus was found in a grave reserved for sacred animals. Since the monster seemed to resemble a monkey, it was probably thought to be of animal origin and was embalmed and buried with other sacred creatures. The birth of such sacred monsters, considered the result of unnatural though not sinful cohabitation, did not lead to persecution of the mother.[2] Crosses of human and terrestrial beings also are found in Greek mythology as centaurs, minotaurs, satyrs, and many other more or less respectable personalities, suggesting that fertility between different species was considered possible in those days.

In contrast to these pagan ideas, the Mosaic and Christian laws condemned relations of man with animals as criminal. With the acceptance of these religious laws the hybridity theory became very dangerous to the mother or the suspected father of a monstrous creature. Many examples could be cited, but I shall limit discussion of this unpleasant period to two events which prove the survival of this theory and its cruel consequences to more recent times.

For the first example I am indebted to Professor Walter Landauer of Storrs, Connecticut, who expects to report on it in detail. The story is told in the *Records of the Colony and Plantation of New Haven, From 1638 to 1648*.[8] Three years after the founding of the colony, a monstrous pig was born (in 1641) that had "butt one eye in the midle of the face" and over the eye "a thing of flesh grew forth and hung downe, itt was hollow, and like a mans instrum' of gen'ation." This was obviously a cyclopic pig with a proboscis, a malformation not rare in that species. However, to the good people of New Haven, cyclopia was not known as a spontaneous defect in pigs, and they attributed the birth of this monster to the "unnatureall spell and abominable filthynes" of a servant, George Spencer, who had "butt one eye for vse, the other hath (as itt is called) a pearle in itt" and closely resembled the eye of the miraculous pig. The court procedures, the confessions, and retractions, as well as the testimonies are recorded

in great detail. This trial continued from 1641 to 1642, but finally the prisoner was executed on April 8, 1642, after the cyclopic sow had been "slaine in his sight, being run through wth a sworde." On reading this trial one realizes that the hybridity theory of India and Egypt was, with modifications, imported to this country—but also, the proceedings demonstrate that "brain washing" was not invented in recent times.

It is impossible to estimate how many persons became victims of the hybridity belief during the Dark Ages. That punishment was probably not rare may be gathered from the second example to be cited. The Danish anatomist, Bartholin, mentions in his writings that a girl who gave birth to a monster with a "cat's head" was burned alive in the public square of Copenhagen "ob lasciviorem cum fele jocum." This happened in 1683 in a civilized country, only 276 years ago. The fact is reported by Bartholin without criticism or expression of disapproval.[13] The event occurred 12 years after Niels Stensen, another Danish anatomist, had demonstrated his teratologic knowledge by an admirable description of a fetus with tetralogy of Fallot.[23] This is an illustration of the fact that science and coarsest superstition can thrive side by side in the same country at the same time.

Comparisons of malformations with structures seen in animals have been continued to our own times in many languages by the use of such expressions as harelip, bec-de-lièvres, gueule-de-loup, Hasenscharte, Wolfsrachen, phocomelia, and others.

Related to the hybridity theory is the belief that malformations are the result of the association of human beings with demons, witches, and other evil consorts. Especially in Europe during the fifteenth and sixteenth centuries it was believed that the world was populated by demonic creatures, sorcerers, witches, incubi, and succubi who plagued human beings waking or asleep. When a deformed child showed any sign which resembled the imaginary features of the devil, a demonic origin was suggested. Hairy nevi, ichthiosis, club feet, shortening of the upper extremities, long and deformed ears, syndactylism, and similar anomalies could be interpreted as signs of satanic origin. Many pamphlets and broadsheets are existent which show such creatures of unmistakable demonic origin.[9] In these pamphlets the devilish creature shows wings in place of arms, illustrating probably such malformations as phocomelia, syndactylism, or polydactylism. Repeatedly one hears of a monster born in Crakow, Poland, in 1543, whose head was comparable to that of a cat. It had fiery eyes and on each shoulder two small monkey heads. On the arms and knees small dog heads were attached. The fingers and toes were webbed and a tail and a trunk were well developed. The description of this child and his picture were published many times in pamphlets and in books; the monstrosity was ascribed to an evil spirit by some of the learned authors. Whatever the anomalies of this child may have been, they cannot have resembled the description and the pictures reproduced. However, printing and reprinting and a wide distribution made this fabulous child an accepted fact, an example of the power of written or printed records, which with a minimum of factual content can create psychological realities lasting for centuries. In those days demonology with all its ramifications had developed

into a pseudoscience incomprehensible to the modern mind and was exacting many sacrifices of human lives.

Of course, sometimes it was observed that honest and pious women gave birth to monstrous children, and such mothers were not punished like the sinners who were burned at the stake. In many broadsheets still existent such unusual births were interpreted as manifestations of the divine anger aroused by the depravity of the world. Man's haughtiness and arrogance, and particularly his innovations were obviously going too far as intimated by the birth of deformed children. Hollaender[9] gives many examples of pamphlets which compare certain malformations with new and foreign fashions, a clear indication of divine disapproval of the prevailing trends.

In justice to the medieval world, it should be said that execution of the deformed child or of the mother did not originate in those rather recent times. Although there are indications that primitive peoples sometimes kept deformed children, twins, or conjoined twins alive and treated them well,[4] there can be little doubt that among many savage tribes deformed children were quickly disposed of. Infanticide was practiced not only on children with malformations,[7] but also on normals when economic or religious causes demanded it. In certain tribes female infants were endangered; in others, males. Twins were sometimes killed together with their mothers.

Infanticide was widespread among the early Greeks and Romans. It was practiced, according to Aristotle[7] when there were too many children, and Plato advocated it for the inferior or deformed in his *Republic*. However, it was in national-socialist Sparta that infanticide was incorporated in the constitution and practiced for the good of the commonwealth[20]—"Lycurgus was of a persuasion that children were not so much the property of their parents as of the whole commonwealth" and if "puny and ill shaped ordered it (the child) to be taken to what was called the Apothetae a sort of chasm under Taygetus." There the child was disposed of "if it did not, from the very outset, appear made to be healthy and vigorous." With such eugenic measures, the Spartans became a courageous, hardy, and ruthless people, but to art and culture they contributed nothing. This is not surprising since they probably threw into the chasm at Mount Taygetus the Spartan equivalents of such weak children as Newton, Darwin, Voltaire, and Rousseau, who, though puny at birth, made important contributions to a later civilization.[11] Lycurgus would have been surprised to learn that another tiny premature developed into Napoleon Bonaparte, a military commander who would have won the admiration of the most virile of Spartans.

In Rome deformed children were sometimes exposed in the Tiber, and it was particularly hermaphrodites that were chosen as victims and were executed. Other monstrous children also were sacrificed, especially in times of danger or when a catastrophe occurred. When the Roman republic was threatened, Arnus, chief of the Etruscan augurs, ordered that all monstrous children be killed and burned.[2] Thus the treatment of deformed children was often unfavorable among savage and pagan peoples, but the hybridity theory and the demonology of the Middle Ages extended the danger to the mother, neighbors, or other persons not conforming to the customs and beliefs of the land.

VOL
10
195

It would be erroneous to assume that only superstitious and primitive attitudes prevailed in the past and that the ideas which we now have about congenital malformations originated entirely in recent times. Biologic theories and explanations of deformities that appear rational to us date back to early periods of history. Some ancient concepts are rather similar to our own, although some of the basic facts of human reproduction were then unknown and the terminology has changed. The Greek philosopher, Empedocles, who lived in the fifth century B.C., was apparently so impressed by the existence of human monstrosities that he considered them as the forerunners of man as we know him. He developed a theory of evolution which was somewhat related to the modern one. It assumed an accidental appearance of disjointed organs which formed a variety of combinations and permutations with survival of the fittest. On the earth "many heads sprung up without necks and arms wandered bare and bereft of shoulders. . . . Eyes strayed up and down in want of foreheads. . . . Solitary limbs wandered, seeking for union. . . . Many creatures with faces and breasts looking in different directions were born. . . . Some, offspring of oxen with faces of men, while others, again, arose as offspring of men with the heads of oxen, and creatures in whom the nature of women and men was mingled, furnished with sterile parts. . . . But as divinity was mingled still further with divinity, these things joined together as each might chance, and many other things besides them continually arose. . . ." The monstrous forms which came into being by the fortuitous union of these parts soon became extinct, but finally the fit formations survived as animals and men.[2, 5, 16]

Aristotle had a surprising knowledge of teratologic facts. He knew of redundance and reduction of the fingers, toes, hands, and feet. He knew of imperforate anus, absence of the gall bladder, spleen, or one kidney; he mentioned situs inversus, and cases of two spleens. He knew that milder malformations can occur in viable animals and that those which depart more severely from the normal do not live beyond the newborn period. Aristotle's description of a hermaphrodite or pseudohermaphrodite agrees perfectly with present-day observations. His knowledge of, and approach to, malformations represent the height of ancient teratology. The fact that his statements were uncritically repeated and passed on for centuries without verification cannot be held against him. His writings on embryology and teratology were not surpassed for many centuries.

Pliny the Elder, who lived in the first century A.D., mentions many teratologic curiosities in his *Natural History*. Unfortunately, he was an uncritical writer, so that some fantastic statements are intermingled with pertinent observations and excellent descriptions. He knew that some moles and birthmarks can be transmitted through several generations. He relates that in the Lepidus family three children were born with a membrane over the eye. He knows of sex reversal and hermaphroditism. And he gives a brief description of a boy with precocious sex development and premature growth who was carried off by a sudden attack of paralysis when he turned three. Such cases still occur and one is tempted to venture a diagnosis 1,900 years later. But in contrast to Aristotle, Pliny had no general concepts or explanations for the anomalies he described.

New ideas were also lacking during the following centuries and the decline of teratology as a biologic science during the Middle Ages has been illustrated by the superstitions mentioned before.

It was not until 1,600 years after Pliny, when Harvey's *Exercises on the Generation of Animals* appeared in 1651, that a new biologic explanation was introduced into teratology, the explanation of congenital malformations by arrest of embryonic development. William Harvey had an opportunity to study reproductive processes by direct observation and he acquired a good knowledge of embryology derived from hen's eggs and particularly by dissections of deer, which were available to him during the hunting expeditions of his patron, Charles I. In the treatise concerned with reproduction the following sentences are found: "In the foetuses of all animals, indeed that of man inclusive, the oral aperture without lips or cheeks is seen stretching from ear to ear; and this is the reason, unless I much mistake, why so many are born with the upper lip divided as it is in the hare and camel, whence the common name of harelip for the deformity. In the development of the human foetus, the upper lip only coalesces in the middle line at a very late period."[2] Here for the first time, apparently, the idea of arrest of development during embryonic life is mentioned as a cause of congenital anomalies, and with this thought a new period of teratology began. Although the principle of embryologic arrest was expressed by Harvey, it was not applied by many during the next 150 years, after which this explanation for congenital malformations became most popular.

This brings us to the nineteenth century which represents a peak in the area of teratology. Then malformations were intensively studied in man, and brilliant experiments in lower animals began to supplement morphologic investigations. The teratologists of the past century were generally concerned with the study of environmental modifications of embryos, as germinal concepts had not yet gone beyond the stage of speculation. But in 1866 there appeared a small publication by a monk called Gregor Mendel[14] on plant hybrids which had no direct connection with malformations yet proved of fundamental importance for our science. Again, the seed did not germinate for 40 years until it was found that some malformations in man and in animals are transmitted like normal traits of the garden pea. Thus, genetic explanations made their appearance, indicating that in many instances the origin of malformations dates back to events which occurred generations before conception of the deformed child.

The ancient history of teratology does not teach us much about the origin, prevention, or treatment of congenital malformations; but it tells us a great deal about the human mind and its reactions to unexplained phenomena. If an abnormal child is born in a family or tribe, man insists upon an explanation. He does not put off his question and does not wait until science gives him a satisfactory answer. Considering the millenia of observations, explanations have been relatively few, and most of the theories of the past are now considered superstitions. Knowledge of the old and deep-rooted superstitions is of some practical importance since ancient beliefs often plague the parents even today, as they interpret them as portents or punishments. Such beliefs should be brought out into the open, discussed, and treated as a possible source of emo-

tional disturbances. But let there be no mistake—as long as we cannot explain to a mother why *her* child is deformed, she will retain her own explanation and remain unconvinced by our general statements. It is not easy to define the border line between a superstition and a theory. Superstitions generally are based on a disproportion between knowledge and belief. Since even in our time knowledge concerning the etiology of congenital malformations is limited, and beliefs are free, we must be aware of the possibilities that we can create new superstitions in place of the old. For instance, the fascinating animal experiments to be discussed later in this conference may create new superstitions if applied uncritically to human conditions. If certain congenital malformations can be attributed in certain animals to dietary deficiency, anoxia, cortisone, or genetic constellations, one must not conclude without further proof that comparable malformations in man are due to similar adverse conditions. Such premature conclusions, usually not drawn by the experimentor but by a reader whose imagination and beliefs exceed his knowledge, can create superstitions in modern garb. If such a reader is also a writer with access to medical or popular journals, his unfounded beliefs are carried to millions, whereby new superstitions are established. Considerations of the past have shown how inflexible statements become, once they are written down on clay tablets, papyrus, or paper. A single observation of an abnormal child born to a mother who had been in an automobile accident, becomes, if reported in a popular magazine, psychologically, a hundred thousand observations which seem to establish a causal relationship between the two events. The whispered word is powerful, but the written word endures.

History has shown that scientific knowledge can coexist with crude credulity and primitive reactions to the deformed. In our own time we have witnessed how in the Third Reich the discoveries of genetics were distorted, misinterpreted, and transformed into a law which entirely failed to prevent defective offspring. To popularize insufficient knowledge does not pay.

Superstitions disappear quickly when replaced by scientific theories which lead to preventive or curative measures. When the "King's Evil," the "French disease," and childbed fever, which only yesterday also were surrounded by crude superstitions, were eliminated by scientific methods, the superstitions associated with them disappeared rapidly. Since malformations and monstrosities will be with us for some time to come, a knowledge of the beliefs about their origin, ancient or modern, ridiculous or rational, is still a necessity in dealing with the parents and the public.

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VOL
10
195

CAUSES OF CONGENITAL MALFORMATIONS IN HUMAN BEINGS

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OL.
10
959

THE causes of malformations are multitudinous and complex, and though a great deal of effort has been spent in searching them out, our knowledge of them is still regrettably fragmentary. The purpose of this paper is to summarize briefly what we know about the causes of malformations in human beings, and then to review, albeit superficially, the approaches by which such knowledge has been gained, or may be gained.

WHAT WE KNOW

The term "congenital malformation" will be used to denote gross structural abnormalities present at birth. Admittedly it can be argued that cellular abnormalities such as spherocytosis and molecular diseases such as sickle cell disease are malformations at the cellular and molecular levels, respectively. However, it is felt that the term, when used at these levels, becomes so all-inclusive that it is no longer meaningful. Certainly, as commonly used, the term refers to anatomic abnormalities as observed at the supracellular level.

Congenital Malformations With a Specific Environmental Cause.—Some idea of the complexity of the problem may be given by the fact that although the search for environmental teratogenic factors has been long and intensive, only five environmental agents have so far been clearly implicated as causes of congenital malformations in human beings.

The first of these to be identified was *radiation*, either therapeutic[39] or atomic.[47] Little attention was paid to the first reports of this environmental teratogen, but the discovery that maternal infection with *rubella* during pregnancy might lead to a characteristic syndrome of defects in the resulting child[18,58] caused a great upsurge of interest in environmental causes of malformations—an upsurge that was abetted by Warkany's notable demonstration[66] that a specific maternal dietary deficiency during pregnancy was teratogenic in rats. Some years later a second infectious agent, the *toxoplasma organism*, was found to be teratogenic in human beings.[11]

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Reasoning from the discovery in experimental animals that acute *folic acid deficiency* during pregnancy might terminate the pregnancy (and, if not, might cause malformations in the embryos), Thiersch[59] used aminopterin to induce therapeutic abortions and found that in all three cases where the treatment failed the embryos were malformed. Similar cases have been observed by others,[32] and it seems likely that this association is causal rather than coincidental. More recently another iatrogenic teratogen has been identified—synthetic *progestins* used in the treatment of threatened or habitual abortion may occasionally produce abnormalities of the phallus in female babies.[68]

Identification of such teratogenic agents is important, since it reminds us that the human embryo is not entirely insulated from the external environment, and since malformations due to these agents are almost entirely preventable. On the other hand, they constitute only a small proportion—perhaps no more than 1 per cent—of all malformations, so that their prevention would reduce the total malformation load by only a small amount. Furthermore, even where an environmental agent has been shown to be teratogenic, it does not produce malformations in every embryo exposed to it. The risk of malformation is estimated as between 5 and 30 per cent when maternal infection with rubella occurs in the first trimester of pregnancy.[20] Why do the unaffected embryos escape? Is it because they are not in a susceptible stage at the time of infection, or do they have resistant constitutions, or is there some other reason?

It should also be mentioned that a number of environmental agents that one might suspect of being teratogenic do not seem to be so. Efforts to determine whether general malnutrition increases the malformation rate have not produced any conclusive results,[55,64] and there is no convincing evidence that pernicious vomiting,[50] attempted abortion,[67] except by the use of folic acid analogues, or anoxia[65] increases the frequency of malformations in human beings. In some of these the data are still not sufficient to rule out teratogenicity altogether, but it seems clear that they cannot account for more than a small minority of defects, if any. Data on viruses other than rubella are scanty, and it would be interesting to see if modern epidemiologic studies now possible on a large scale will lead to the identification of other viral teratogens. So far there is little to suggest that they will.

Congenital Malformations With a Specific Genetic Cause.—Some malformations are clearly the result of abnormality in a particular pair of genes. A partial list of these has been presented elsewhere.[16]

Those due to *dominant* genes can be easily identified by the fact that they can be traced back directly from affected child to affected parent for many generations, except where they arise by fresh mutation. The situation is more difficult when the gene shows reduced penetrance, i.e., when there is no clinical abnormality in some carriers of the gene.[56] If penetrance is lowered very much, it becomes difficult, if not impossible, to distinguish this from other complex modes of inheritance.[38]

Conditions due to dominant genes are kept in the population by mutation and by reproduction of affected individuals, and they are reduced in frequency

VOL. 10 195

by selection, the fact that affected individuals have a lower-than-average probability of having children.

Malformations due to rare *recessive* genes are harder to identify. For one thing, the parents and collateral relatives of an affected child are almost always unaffected. Furthermore, even though the condition is genetic, most patients with such a malformation do not have affect sublings, since siblings of an affected child have only one chance in four of being affected, and families tend to be small in modern society. Consanguineous parentage may sometimes provide a clue,[14] but it is usually impossible to demonstrate a genetic basis for the condition in question except by statistical analysis of pooled data.[41] These malformations are also kept in the population by mutation and by reproduction of carriers of the gene and are reduced in frequency by selection. Since selection acts mainly on the affected persons and since most of the abnormal genes occur in unaffected carriers, selection is less effective in recessive than in dominant inheritance.

Types of malformation with a clear-cut genetic basis are individually rare, and collectively account for only a small proportion of the malformation load—probably well under 10 per cent.[61]

Congenital Malformations With No Identified Specific Cause.—In the great majority of malformations no specific causal factor can be demonstrated at present. The situation is complicated by the fact that within any single clinical category of defect there are likely to be cases due to a wide variety of causes, and it is usually impossible to tell, from the end result, what particular combination of factors was responsible for the defect in any one case. However, it is possible to establish some statistical correlations that may at least be guides as to where one might look for specific factors.

Environmental correlations: Correlations between frequency of defect and such things as season of birth, social class, and parental age have been demonstrated for a number of malformations, and these will be discussed in more detail later. So far this sort of analysis has not led to the identification of any specific causal factors, although it suggests that there must be some. What is it about the lower social classes that makes them more prone to have anencephalic babies, for instance? It is nutritional deficiencies, or greater exposure to infections, or genetic differences, or what?

Familial tendency: A number of malformations, such as tracheoesophageal fistula, almost never occur in more than one child of the same parents. Others, such as most types of congenital heart disease, show a slightly increased tendency to recur in sibships.[24] Still others, such as harelip, cleft palate,[12] anencephaly, spina bifida aperta,[44] and clubfoot,[8] show a definite tendency to occur more often in the relatives of affected persons than in the general population. This raises the question of whether such a correlation is due to genetic, or to familial environmental factors, or to a combination of the two.

The fact that in *twins*, where at least one has a particular type of defect, monozygotic pairs are more often concordant (both affected) than dizygotic pairs are suggests that genetic factors are causally involved, since monozygotic twins are genetically identical and dizygotic twins are not. However, it could

be argued that monozygotic pairs are more similar than dizygotic pairs in their intrauterine environment, as well as their heredity, so this evidence is not conclusive.

Evidence from *experimental animals* suggests strongly that some types of "sporadic" congenital malformations are genetically influenced. In the inbred A/Jax mouse strain, for instance, about 15 per cent of the newborn young have a cleft lip, but none have microphthalmia. In the C57BL/6 strain, on the other hand, about 8 per cent of the young have microphthalmia, but none have a cleft lip. Clearly, it is the genes that determine that one type of embryo is prone to cleft lip and the other to microphthalmia, but in neither case is the genetic basis a simple one. Furthermore, the presence of nongenetic factors is suggested by the fact that some animals in a litter have the defect and other genetically similar animals growing in the same uterus do not. It would seem that these environmental factors must be fairly subtle, since they are not readily identifiable. If so, the action of the genes may be to make the embryonic A/Jax lip, on the one hand, or the C57BL/6 eye, on the other, susceptible to developmental disturbance by relatively minor intrauterine variations.[13] Such a hypothesis would also account for situations where the concordance rate for a congenital defect is higher in monozygotic than in dizygotic twins, but still well below 100 per cent.

Neel[40] has recently suggested that at least some malformations in human beings may represent what Lerner[28] has termed "phenodeviants." This concept stems from the observation that (for some species, at least) it is advantageous for a population to consist largely of individuals that are heterozygous (i.e., have the two members of a gene pair somewhat different) for many pairs of genes or gene-complexes. In order to achieve this, some individuals must necessarily be homozygous (alike) at too many loci for their own good, and these, the hypothesis states, will be relatively "unbuffered," i.e., will be deflected from the normal developmental path by relatively minor environmental fluctuations.

Thus it seems clear that most congenital malformations are the result of complex interactions between multifactorial genetic and environmental systems. Any single clinical category is likely to include a variety of etiologically different types. Obviously, clarification of the causes of congenital defects will not be simple.

METHODS OF INVESTIGATION

The Epidemiologic Approach.—The epidemiologic approach studies variation in frequencies of malformations with respect to a variety of environmental factors, exclusive (for this discussion) of familial relationships.

Prevalence: To begin with, it is useful to know how often congenital defects occur in the general population, how many there are of each particular type, how many are multiple, and in what proportions the various possible combinations of defects occur. As recently pointed out by Neel,[40] there is a sad lack of adequately large series presented so that such information can be extracted for comparison with other series. Part of the trouble lies in the fact that many malformations are not readily diagnosed at birth; McIntosh and associates[30]

have shown that less than half of the malformations diagnosed in a group of children followed from birth to one year of age were discovered at birth.

Regional variation in frequency: There is also a lack of reliable data on variation with geographic region, except for a few conditions such as anencephalus which are so obvious that the diagnosis could not be missed at birth. Penrose[44] has pointed out the striking regional variations in frequency of anencephalus (which is, for instance, twenty times as high in Belfast as in Paris), but there is no evidence as to what specific factor in the Belfast environment makes it so "anencephalogenic."

Seasonal variation: A number of malformations show a distinct seasonal variation in frequency. Record and Edwards,[51] for instance, have noted that, in Birmingham, children with congenital dislocation of the hip are twice as likely to be born in winter as in summer. They suggest, tentatively, that seasonal differences in clothing habits might account for this (it would be useful to know if seasonal differences occur in other climates), and state that the frequency of this malformation could be decreased by as much as 50 per cent by arranging conception in late autumn!

Edwards[10] has reported a marked seasonal variation in the frequency of anencephaly in Scotland, with an increase in October to February. He could find no evidence of association with epidemics. Thus no specific factor has been identified as a cause of the seasonal variations in malformation frequency.

Social class: Edwards[10] has shown that in Scotland the frequencies of anencephalus, spina bifida aperta, and hydrocephalus are markedly increased in the lower social classes, but again no specific factor was implicated. Edwards points out that social class is a familial factor, and suggests that "The marked environmental influences cast doubt on the necessity of advancing genetic causes to explain familial concentrations." It is difficult to see, however, how environmental variations of the order of magnitude reported could account for the relatively high recurrence risk (about 5 per cent) in siblings.

It might be mentioned here that the Scottish vital statistics system appears to be the only one at present reporting data suitable for analysis with respect to social class, parity, parental age, legitimacy, etc. from which tendencies such as those mentioned can be demonstrated. There is a great need for comparable data from other countries. Canada may possibly modify her present system to this end, with the additional advantage that family relationships would be tabulated as well.[42]

Parental age: Correlations of malformation frequency with parental age could be considered either with the environmental or the genetic factors. Penrose[46] has pointed out how variation with maternal age (as distinguished from that occurring with paternal age as well) may depend on physiologic changes in the aging mother, acting directly on the embryo or indirectly, through the production of mutations. The most striking example of this is Mongolian idiocy.[45] Correlations with paternal age (as distinct from those with maternal age) suggest that some portion of the defects concerned results from mutations that occur as the result of copying errors during gene reproduction. This type of correlation

has been demonstrated for achondroplasia[46] and, more recently, for acrocephalosyndactyly.[6]

Parity: Correlations with parity (as distinct from those with increasing parental age) have been reported for a number of congenital defects. Edwards,[10] for example, showed that anencephaly was 40 per cent more common in first than in second pregnancies. However, there are so many biases involved in measuring parity effects, such as the tendency of parents not to have further children after having a malformed one, that their causal significance is often suspect.[31]

Correlation with epidemics: If congenital malformations can be caused by infectious agents, one ought to see epidemics of malformations following epidemics of infectious diseases, and this, indeed, was the way the teratogenicity of rubella was discovered.[18] So far, however, no other teratogen has been identified by this approach.

Correlation with other environmental extremes: One might expect to identify environmental teratogens by looking for an increase in the frequency of malformations in areas where the suspected teratogen was present in unusual amounts. This approach has so far been unproductive. The lack of evidence that malnutrition is teratogenic has already been mentioned. Evidence that the malformation rate was elevated in populations living at high altitudes would not necessarily implicate hypoxia, for instance. One would also have to consider other ways in which the population at risk differed from populations at lower altitudes, e.g., in their exposure to radiation, in their genes, in the mineral content of their water, etc.

In summary, then, the epidemiologic approach has led to demonstration of correlations between the frequency of congenital defects and a variety of environmental variables, but has not (with the exception of rubella) led to the identification of any specific teratogenic factors. This suggests that the causes of congenital defects are *multiple complex*, and *subtle*.

The Genetic Approach.—This section will review methods designed to detect genetic factors in the causation of diseases.

Pedigree analysis: Pedigree analysis is necessary to establish which malformations are inherited in a simple Mendelian manner (page 98, paragraph 4). Thus, to cite only two of many examples, it has been shown that the lobster claw defect is often the result of a single dominant gene,[5] and that the Ellis-van Creveld syndrome has a familial distribution suggestive of autosomal recessive inheritance.[34]

Furthermore, pedigree analysis may enable the investigator to pick out specific genetic types from the miscellaneous group usually included in one clinical category. For instance, in a small minority of patients with cleft lip and/or palate, the defect is due to a dominant gene which causes cysts of the lower lip and, in about half the carriers of the gene, cleft lip and/or palate as well.[62] It is important to be able to pick out these cases, as the risk of recurrence of the defect in such a family is much greater than it is for the usual type of cleft lip or palate.

The contingency method: The contingency method is designed to detect a familial tendency, if any, of the character being investigated, by selecting affected persons (probands) in a way which is not influenced by whether they have affected relatives and by measuring the frequency of affected individuals in various groups of relatives of the probands. If the frequency is higher, the closer the relationship to the proband, a familial tendency is demonstrated. Then the investigator is faced with the problem of finding out whether this tendency is due to genes or to familial environmental factors.

Information of this sort is available for a number of malformations and provides empirical risk figures concerning the probabilities that future siblings, offspring, etc. of affected persons will be affected, which are useful for counselling.[15,16] For instance, siblings of a child with harelip have about a 5 per cent chance of having a harelip, but their chances of having some other sort of congenital defect do not seem to be increased. The results of sibling studies also argue against the idea sometimes expressed that malformations are one aspect of a spectrum of reproductive error ranging from sterility and early abortion to birth injury. If this were so, one would expect that, rather than just an increased frequency of the same type of malformation in the siblings of malformed children, there would be an increased number of abortions, stillbirths, and malformations in general in such families, and this has not been demonstrated.[63]

The contingency method may also be useful in *establishing etiologic associations* or distinctions. The fact that spina bifida aperta occurs with an elevated frequency in the siblings of propositi with anencephaly[44] suggests that even when the two defects do not occur in the same individual they are etiologically related. Conversely, the fact that the frequency of cleft palate (without cleft lip) is not increased in the siblings of children with cleft lip (with or without cleft palate) and vice versa suggests that the two entities are etiologically distinct.[12]

A third application of the contingency method is in the detection of *formes frustes*, or microforms of the malformation in question, that might indicate which relatives of an affected person are carrying the genetic predisposition. This approach has been applied successfully in a number of genetically determined biochemical defects[21] and in a few malformations with a simple genetic basis, e.g., the brachyury in the parents and other heterozygous relatives of patients with a rare form of chondrodystrophy.[7] However, in spite of numerous attempts, no convincing demonstration of *formes frustes* occurring with an elevated frequency in relatives of affected persons has been presented for any of the common malformations.

The twin method: The basis of the twin method has already been mentioned (page 99, paragraph 5). The methodology and the difficulties in interpretation of results have been reviewed elsewhere.[33,35,48] For most of the common malformations (with the exception of congenital heart disease[60]), the concordance rate is considerably higher in monozygotic twins than in dizygotic twins, but (with the possible exception of Mongolism[1]) an appreciable proportion of monozygotic twin pairs are discordant. Since monozygotic twins are genetically alike and dizygotic twins are not, the increased concordance in monozygotic pairs may signify that there is a genetic basis for the defect in question. On the

VOL.
10
1959

other hand, it could be argued that monozygotic pairs have a more similar intrauterine environment than dizygotic pairs and that this is the reason for the difference in concordance rate. If this were so, monochorionic monozygotic pairs might be expected to have higher concordance rates than dichorionic monozygotic pairs. It would be useful to have data bearing on this point.

The consanguinity method: Because persons who are related are more likely than unrelated persons to have some genes in common, evidence of an increase in malformations in the offspring of consanguineous matings suggests that recessive genes may be the cause of some malformations.

The problem may be approached in two ways, both useful, but for somewhat different reasons:

a. If one starts with a rare defect or syndrome and finds that there is an increased frequency of consanguinity among the parents of affected children, this is a clue that the condition may be recessively inherited. Thus the fact that the first two reported cases of the Ellis-van Creveld syndrome occurred in the offspring of (different) first-cousin matings led Ellis and van Creveld to suggest a recessive gene pair as the cause of the condition some years before the first familial cases were reported.[34]

b. On the other hand, one may observe the frequency of malformations in the offspring of consanguineous parents. Any increase in the frequency of congenital malformations above that in the general population will be a measure of the contribution that recessive genes make to the malformation load of the population. Because of the rarity of consanguineous matings, such data are difficult to obtain in adequate numbers. By far the largest series to date is that reported by Schull[52,53] on a Japanese population. He found a slight increase in the malformation frequency in the consanguineous group, most of the increase being due to multiple malformations. Whether these represent a number of hitherto unrecognized recessively inherited syndromes or some more complicated result of increased homozygosity is not entirely clear, and more data of this sort are needed.

Racial comparisons: Differences between races in frequency of a congenital malformation suggest a genetic bais for the defect, provided it is not due to environmental differences between the races, and this may be very difficult to prove. Furthermore, there is very little reliable information on frequencies of malformations in different racial groups. Neel[40] points out that "The total impact of major congenital defect upon Caucasian, Mongolian (Japanese), and, possibly, Negro populations appears to be very similar," but that there are "many significant and even striking differences as regards the frequency of specific malformations." For instance, harelip and/or cleft palate is more frequent in Japanese than in Caucasian populations, and more frequent in Caucasian populations than in (American) Negroes. For polydactyly, on the other hand, the order is Negro > Japanese > Caucasian. Furthermore, combinations of defects occurred more often than would be expected if the various defects were distributed independently, and there were interesting features about the patterns of association. For instance, in multiple defects involving, as one component, malformation of the central nervous system, harelip and/or cleft palate occurred more

frequently as an associated defect in the Japanese (39 per cent) than in Caucasians (13 per cent). The preponderance of harelip and/or cleft palate in the Japanese is greater in multiple malformations than in single malformations. It is as if the Japanese had a lower threshold of abnormality for harelip than the Caucasians, so that a developmental disturbance causing a central nervous system malformation would be more likely to push a Japanese than a Caucasian embryo over the harelip threshold as well. These findings are compatible with the idea previously mentioned (page 99, paragraph 5) that some malformations may be phenodeviants.

Cytologic studies: Recent advances in cytologic techniques have made it possible to study human chromosomes in much more detail than ever before, and such studies may make valuable contributions to our understanding of some malformations. Already there is evidence[27] that Mongolian idiocy is characterized by a supernumerary chromosome. Another cytologic advance that is rapidly increasing understanding of malformations of the genital tract[19] was initiated by the observation of Barr and associates,[3] that the "chromosomal sex" of cats could be determined by observation of somatic cells. Now it appears that certain types of intersex may be the result of chromosomal imbalance—for instance, Klinefelter's syndrome may be associated with a Y chromosome in what would otherwise be (XX) females.[23] It will be interesting to see how many other malformations are due to chromosomal excesses or deficiencies.

Recent advances in tissue culture techniques have also opened up new approaches to the malformation problem. It is now possible to grow mammalian cells from different tissues in culture and analyze their properties by methods formerly limited to the study of microorganisms. Thus the effects of a mutant gene on the biochemistry and physiology of cells from different tissues, at various stages of development, can be studied. This is being done for such conditions as phenylketonuria,[49] and there seems to be no reason why it could not be done for embryos with hereditary malformations. This might throw light on the mechanisms by which mutant genes alter development. However, it does not seem likely that any clear-cut biochemical abnormality analogous to those found in the "inborn errors" will be identified in the great majority of congenital malformations, since most of them do not have a simple genetic basis, and even in those that do, the somatic biochemical abnormality may well be transient.

Tissue culture is also providing a useful medium for the study of embryonic mechanisms. Among many examples are cited the work of Auerbach and Grobstein[2] on tubule-mesenchyme inductive relations in the developing kidney, and of Bennett,[4] who is studying the effects of a mutant gene on the neural-tube-somite inductive relationships in the mouse. In the latter case the action of the gene in interrupting development of the axial system cannot be attributed either to disturbance of the neural tube's inductive capacity or to the somites' competence to react—an indication that embryologic analysis of mammalian development and its aberrations will not be simple. Cells organized into tissues have properties that transcend the properties of the individual cells, and I suspect that the morphogenetic behavior of tissues (and how it goes wrong) cannot be described solely in terms of the biochemical and biophysical properties of the individual cells which will make up the tissues.

The Embryologic Approach.—Space and my qualifications do not permit more than brief mention of the various embryologic approaches to knowledge of malformations. Knowledge of the abnormal must be based on knowledge of the normal, and there is still much to be learned about normal human development. The difficulty of obtaining young human embryos in suitable condition has retarded progress in this field, although increasing use is being made of embryos obtained by abortion in countries where this procedure is practiced legally. It is, of course, even more difficult to obtain suitable abnormal embryos for analysis, and each one examined can only contribute information about one fleeting stage in a continuing process. Nevertheless, a good deal of useful information can be gained by careful examination of the available material—for instance, the evidence that overgrowth of the neural cord can be a cause of rachischisis.[43]

It is also necessary to describe the developing embryo in biochemical terms, and progress is being made in this direction both in humans and experimental animals. There will be no attempt, in this paper, to discuss the extensive work in experimental embryology and developmental genetics relevant to the problem of human malformations. The reader must be referred elsewhere for a discussion of the growing interest in antigens as possible developmental regulators,[9] of the use of mutant genes as embryologic tools by which specific developmental processes can be altered and the developmental results studied,[17] and of the developmental effects of environmental agents applied directly,[25] or through the mother, to the growing embryo.[37,69]

In spite of the rapid growth of knowledge in the field of experimental teratology, there has been very little legitimate carryover of findings in this field to the problem of human malformations. Each new discovery in the experimental field raises the possibility that it may have some clinical significance, but before its relevance to human beings is accepted there must be clinical evidence of its applicability. Examples of legitimate carryover include the mounting evidence that folic acid antagonists, known to be teratogenic in rodents, may cause malformations in human beings as well.[59] Similarly, Miller,[36] reasoning from the fact that rib anomalies occur in mouse embryos with axial system defects following maternal fasting during pregnancy, found an elevated frequency of rib anomalies in human babies with axial system defects. On the other hand, claims that hypoxia[22] and adrenal corticoids secreted in response to maternal stress[57] are teratogenic in human beings remain unsubstantiated by reliable evidence.

Pregnancy Studies.—Evidence for the teratogenic activity of specific environmental factors might be expected to come from studies of the gestational experiences of mothers giving birth to malformed children and to normal children, respectively. Such studies may be grouped in two main categories, retrospective and prospective, each with its advantages and disadvantages.

Retrospective studies: The retrospective method begins with the malformed child, and, by inquiry from the mother and/or her medical history, seeks to measure the frequency of various events in the gestational history. If a certain event is stated to happen often in more pregnancies giving rise to malformed children than in pregnancies giving rise to normal children, the factor in question is sus-

pected to be teratogenic. This is the method by which Gregg and Swan[18] identified rubella as a teratogen. Apart from this, however, the method has so far been rather unproductive. Part of the reason for this is the difficulty of obtaining satisfactory control data. Two main biases must be dealt with.

Confusion of cause with coincidence is a source of error which, if recognized, is relatively easy to avoid. When an environmental agent is known to be teratogenic in experimental animals, it is tempting to suppose that, when the factor occurs during a human pregnancy that results in a malformed child, the factor is the cause of the malformation. Such a conclusion, based only on individual case reports, is quite unjustified. Proof of a causal association requires evidence that the factor occurs more often in pregnancies giving rise to malformed children than in pregnancies giving rise to normal children. To demonstrate this, unfortunately, is not easy, because of another type of bias.

Maternal memory bias is a source of error most difficult to control. The mother of a malformed child is likely to try hard to find a "reason" for the child's defect in the events of the pregnancy. Thus the mother of an abnormal child will be more likely to remember unusual events during the pregnancy than will the mother of a normal child. She may be abetted in this by the tendency of the investigator to look harder in the former case than in the latter. This source of bias may be virtually impossible to control, but it should at least be taken into account. Failure to do so may lead to unjustified conclusions, e.g., that maternal emotional stress is a cause of cleft palate.[57] If the bias is recognized, it may be possible to obtain useful information by this approach indirectly. For instance, one may compare frequencies of various prenatal factors for different types of defect. An increase due to memory bias would be expected to be similar for all types, but any factors that were etiologically important would presumably have an elevated frequency only in the types of defect with which they are causally associated.[51] It is also possible to obtain a rough estimate of memory bias by comparing the frequency of the prenatal event in question in malformed probands and their siblings and in nonmalformed probands and their siblings.[13]

Thus the retrospective approach is by no means useless, and, if treated with proper caution, may provide leads as to what to look for by the prospective approach. For instance, the intriguing evidence of Langman and associates[26] that malformations may be associated with abnormalities in the mother's serum proteins stemmed largely from retrospective studies and is now being tested by the prospective approach.

Prospective studies: The prospective approach begins with mothers, preferably early in pregnancy, and obtains the desired information before the state of the child is known. This removes completely any maternal memory bias, which is a great advantage.

Prospective studies are necessary in order to establish the frequency with which exposure to a teratogen is followed by a malformation. Following the discovery of rubella's teratogenic properties, for instance, it was at first thought that the risk of the embryo being abnormal, following first trimester infection with rubella, was close to 100 per cent. This was because cases were usually selected retrospectively, by the fact that the child was abnormal. Prospective

studies place the risk of malformation following maternal rubella in the first trimester much lower than this—estimates now varying from around 5 to 30 per cent.[20]

The main disadvantage of the prospective approach is the enormous number of cases that must be studied in order to get enough data for statistical analysis, particularly if (as I think should be done) the figures for each type of defect are to be considered separately. About 100,000 pregnancies would have to be studied to obtain 100 cases of cleft lip, for instance, unless the cases were selected by some criterion (such as a previously affected child) that would increase the expected frequency. This, on the other hand, would make the sample unrepresentative.

Another difficulty of the prospective approach is the fact that one must ask the right questions in order to get positive answers. The questions are based on the results of experimental studies, retrospective clinical studies, and personal hunches, and if the right questions are not asked a lot of work may be done without getting any positive answers. Even if the right questions are asked they may not produce results unless the sample happens to contain an unusually high frequency of the teratogen concerned. For instance, McDonald[29] interviewed 3,216 pregnant mothers, of whom only one had rubella in the first trimester, and she had a normal baby. So one of the few recognized human teratogens would not have been recognized in this study, or even in one ten times as large. However, there were some interesting leads in McDonald's study, such as the high frequency of active or arrested tuberculosis, and of laundry work among the mothers of malformed children. I am sure we are all looking forward to seeing the results of other prospective studies, such as Dr. McIntosh's[30] extensive series, to see whether these suggestions are upheld. At present, however, it must be admitted that no teratogenic factors have been identified by prospective studies.

CONCLUSIONS

A minority of congenital malformations have a major environmental cause.

A minority of congenital malformations have a major genetic cause.

Most malformations probably result from complicated interactions between genetic predispositions and subtle factors in the intrauterine environment. There is certainly no one cause, and (almost certainly) no one cure for malformations.

It may be that the genetic factors in the latter group act by making the embryo sensitive to minor environmental variations. If so, one should emphasize less the search for environmental variables and concentrate more on trying to find what it is about the embryo that makes it sensitive to the minor environmental variations. This would seem to hold more hope of preventing malformations than attempts to eliminate environmental insults.

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OL.
10
959

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EXPERIMENTAL STUDIES ON CONGENITAL MALFORMATIONS

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VOL. 10 1959

THE study of congenital malformations by experimental means appears to have been first undertaken by Saint-Hilaire, the elder, in about 1820. It was continued sporadically during the subsequent hundred years by Saint-Hilaire, the younger, Dareste, Féré, and others.[6] In the last 40 years, however, the pace has quickened considerably, and such a volume of literature has accumulated as to make a comprehensive review tedious and time consuming. The purpose of this paper is neither to present an exhaustive coverage of the subject nor to make a critique of any one aspect of it, but to survey the literature in search of valid generalizations and basic principles that may be deduced from the experimental results now at hand.

For this purpose it seems best to limit the survey to experiments on warm-blooded animals, that is, to the birds and mammals. These groups have comparable metabolic processes and respond to many agents in similar ways. During embryonic development, however, they differ in one very fundamental respect. The incubating egg of the birds possesses an inherent supply of nutrients and depends upon the environment only for warmth and a meager interchange of gasses, but it is also immediately subject to any changes in the environment. The mammalian embryo, on the other hand, must receive all its needs for maintenance and growth from the maternal organism that surrounds it and with which it communicates by means of the placenta. The latter exercises a considerable selection over the substances transferred from mother to embryo. The maternal body of mammals under ordinary circumstances, therefore, forms a well-regulated, almost impervious insulation about the embryo. These differences and similarities in the environment of developing birds and mammals should be borne in mind while considering the factors that cause embryos to develop abnormally.

TYPES OF AGENTS USED

A great variety of methods have been employed for the experimental production of congenital malformations. These now number well in excess of 60 and the indications are that the list will continue to grow for some time. Kalter

and Warkany,[66] in a recent review, cited more than 350 references on only the metabolic factors that have been studied for their effects on embryonic development in mammals. An equal number could probably be found dealing with birds, particularly the chicken. Other reviews of the subject have been written by Giroud[32] and Gruenwald.[43]

Physical Factors.—This category is of particular interest because some of the situations referred to in Table I can and do occur in varying degrees during human pregnancy. Of these, however, only x-rays are known to have caused human malformations. Irradiation was the first method used extensively on mammalian embryos, and, since exact dosage measurements became possible,[60] this method has been the most precise teratologic tool available. The dose reaching the embryo can be known within narrow limits, particularly if the embryos are exposed through an incision in the maternal abdominal wall.[133] The time and duration of exposure also are more accurately known, for other agents must be mediated through the maternal body and consequently there is no sharp termination of action when the agent is withdrawn. Because of the precision with which radiations can be applied, results obtained with this method have proved especially useful in formulating the general principles to be presented later.

TABLE I. PHYSICAL AGENTS THAT CAUSE MALFORMATIONS

AGENT	SPECIES	REFERENCE
X-rays	Rat	Hanson,[50] De Nobele and Lams[21] Murphy and de Renyi[84] Job et al.[60] Warkany and Schraffenberger[125] Wilson,[128] Hicks[54]
	Mouse	Kaven,[67] Russell[105]
Hypothermia	Hamster	Smith[109]
	Chick	Ancel[5]
Hypoxia	Mouse	Ingalls et al.[57] Murakami et al.[82,83]
	Rabbit	Degenhardt[20]
	Chick	Grabowski and Paar[39]
Elevated CO_2	Rat	Haring and Polli[51]
Amniotic sac puncture	Mouse	Trasler et al.[118]

Hypothermia has been widely used with the lower animals, such as fish,[112] but it has been difficult to apply with success to warm-blooded animals until recently. Some of the earliest experiments on teratology involved the cooling of chicken eggs during incubation, but the experimental conditions were so poorly controlled, by modern standards, that the results are of limited value.

Hypoxia has attracted much attention as an experimental agent because of the presumed likelihood of its occurrence during human pregnancy, but it must be emphasized that no proved instance of such occurrence is known. In the mammals in which it has been successfully applied (Table I), the yield of malformed young has been comparatively low. It has repeatedly been found ineffective in the rat.

Elevated amounts of CO_2 in the air breathed by pregnant rats have been reported to cause specific cardiac defects. Because of its obvious implications for human teratology, this experimental procedure needs confirmation and further study.

Puncture of the amniotic sac, with escape of amniotic fluid and consequent change in the physical relationships about the embryo, caused malformations in the mouse. This observation was challenged on the basis of failure of human amniocentesis to cause any untoward effects. Actually the two situations were not comparable, either as to the time the procedure was performed (being at a much earlier stage in the mouse than in the human cases) or as to the relative amounts of fluid withdrawn (the quantities in the human cases were negligible). The known association in human pregnancy between excessive amounts of amniotic fluid and malformed fetuses suggests that alterations in amniotic fluid pressure and quantity should be studied further by experimental means.

VOL.
10
1959

Maternal Nutritional Deficiencies.—This class of agents has been quite thoroughly studied in the last 15 years, particularly by Warkany and his collaborators (Table II). It is interesting that of the 10 agents listed 9 are vitamins, with a majority belonging to the B-complex group. Several of the known vitamins, however, are absent. Absence from this list does not mean that other nutrients are not essential for normal development. A great many others are essential and, if not present in adequate amounts, pregnancy fails to occur or to be maintained when it does occur. In fact, with most of the deficiencies found to be teratogenic it was difficult to achieve exactly the right degree of deficiency. There was a very narrow *teratogenic zone* between the degree which permitted normal development and the degree which resulted in complete reproductive failure. In some instances (indicated by an asterisk in Table II), a specific

TABLE II. MATERNAL NUTRITIONAL DEFICIENCIES THAT CAUSE MALFORMATIONS

DEFICIENCY	SPECIES	REFERENCE
Vitamin A	Pig	Hale[46]
	Rat	Warkany and Schraffenberger[123]
		Jackson and Kinsey,[58] Wilson and Barch[132]
	Rabbit	Millen et al.[78]
Riboflavin	Rat	Warkany and Schraffenberger[124]
		Giroud and Boisselot,[33] Leimbach[74]
		de Watteville et al.[127]
*		Nelson et al.[88]
*	Mouse	Kalter and Warkany[65]
Folic acid	Rat	Giroud and Lefebvres[35]
*		Evans et al.,[23] Thiersch[114]
*	Mouse	Runner,[101] Trasler,[111] Tuchmann-Duplessis and Mercier-Parot[120]
Pantothenic acid	Rat	Boisselot,[9] Zunin and Borrone[136]
*		Nelson et al.[91]
Vitamin B_{12}	Rat	O'Dell et al.[95]
Thiamine	Rat	de Watteville et al.[127]
Biotin	Chick	Couch et al.[11]
Vitamin D	Rat	Warkany[122]
Vitamin E	Rat	Cheng and Thomas[12]
General inanition	Mouse	Kalter,[63] Runner and Miller[103]

*Antagonist alone or in combination with deficient diet.

antagonist was needed to obtain the proper level of deficiency. In others, therapeutic doses of the missing vitamin had to be supplied at critical times in gestation to ensure the survival of any offspring. The latter was always the case with vitamin E deficiency and was usually necessary following use of the antagonists. It is clear, therefore, that a deficiency so delicately balanced as that required to achieve teratogenesis with these vitamins is quite unlikely to occur in nature.

Attempts to produce malformations by starving the pregnant mother have been unsuccessful except in the two instances cited in Table II in which mice were used. It is significant in this connection that the mouse quickly develops hypoglycemia when food is withheld.[102] Females of most species soon cease to run sexual cycles when placed on grossly inadequate diets.

Growth Inhibitors and Specific Antagonists.—This group of agents (Table III) includes chemicals variously characterized as antigrowth, anticancer, and antimetabolic substances because in one way or another they all interfere with growth. The first four listed do so by alkylating susceptible radicals on the nucleoproteins of rapidly dividing cells. The remainder, except urethan, do so by substituting for a particular essential metabolite which they closely resemble in chemical structure. Although able to substitute for the needed substance at one stage of a sequence of reactions, they fail to react like the normal metabolite at a later stage. The end result is an impairment of growth and whether the outcome is a localized defect, more widespread malformations, or death of the embryo probably depends upon the distribution and number of cells that have incorporated the masquerading substance into their metabolic equipment. These, together with radiations and some of the vitamin deficiencies, are among the few teratogenic agents the action of which is to any degree understood. The number of alkylating and antimetabolic compounds will probably continue to grow as a result of the extensive screening programs now being undertaken in search for cancer chemotherapeutic agents. The clinical use of such agents obviously involves the danger that they may be applied during early, unsuspected pregnancy.

TABLE III. GROWTH INHIBITORS AND SPECIFIC ANTAGONISTS THAT CAUSE MALFORMATIONS

AGENT	SPECIES	REFERENCE
Nitrogen mustard	Rat	Hoskins,[55] Murphy et al.[86]
	Mouse	Danforth and Center,[19] Thalhammer and Heller-Szöllösy[113]
	Chick	Murphy et al.[86]
Thiadiazole	Rat	Murphy et al.[86]
Triazines	Chick	Dagg et al.[18]
	Rat	Murphy et al.[86]
Other alkylating agents	Rat	Murphy[85]
Urethan	Mouse	Sinclair,[108] Nishimura and Kuginuki[92a]
Azaserine	Chick	Dagg and Karnofsky,[17] Blattner et al.[8]
	Rat	Murphy and Karnofsky,[87] Thiersch[116]
6-Aminonicotinamide	Chick	Murphy et al.,[86] Landauer[72]
	Rat	Murphy et al.[86]
8-Azoguanine	Mouse	Nishimura and Nimura[94]
Thioguanine	Rat	Thiersch[115]
3-Acetylpyridine	Chick	Ackermann and Taylor,[1] Landauer[72]
6-Mercaptopurine	Rat	Zunin and Borrone[135]
2-6-Diaminopurine	Rat	Thiersch[115]
6-Chlorpurine	Rat	Thiersch[115]

Infectious Agents.—Although many have been tested, very few infections have been found effective in producing malformations experimentally, and all of these are viruses (Table IV). This is of interest in view of the fact that the rubella virus is one of only two infectious agents definitely indicted as teratogenic in man. The other agent in man is toxoplasma, a protozoon which appears to invade the developing embryo and prey specifically upon the central nervous system. There is some question, however, as to whether the malformations caused by this agent represent true aberrations of embryonic processes, and therefore are truly developmental in nature, or whether they are pathologic in the same sense as are most of the defects associated with congenital syphilis and other infections in the human newborn.

OL.
10
959

TABLE IV. INFECTIOUS AGENTS THAT CAUSE MALFORMATIONS

AGENT	SPECIES	REFERENCE
Influenza A virus	Chick	Hamburger and Habel[47]
Hog cholera virus (attenuated)	Pig	Kitchell et al.[68]
Newcastle virus	Chick	Robertson et al.[99]

Hormone Injections and Endocrine States.—Hormones are logical suspects as teratogenic agents since they are frequently present in relatively large amounts in the maternal blood stream, and since many of them have access to the embryo by virtue of their ability to pass across the placenta. The effects on the embryo of sex hormones injected into pregnant animals were extensively studied between 1935 and 1945 when much attention was devoted to the subject of hermaphroditism. Probably more important than the description of the various degrees of intersexes produced was the observation that malformations could be caused by means other than arrested growth. Many of the abnormalities were found to result from the retention of structures that normally regress, or from the overgrowth of other structures under excessive hormonal stimulation. Recently other malformations than those of the sexual systems have been reported by Raynaud as following estrogen injection (Table V).

TABLE V. HORMONE INJECTIONS AND ENDOCRINE STATES THAT CAUSE MALFORMATIONS

AGENT	SPECIES	REFERENCE
Androgen	Rat	Greene et al.[41]
Estrogen	Rat	Greene et al.[42]
	Mouse	Raynaud,[98] Nishihara[92]
Insulin	Chick	Landauer,[73] Duraiswami[22]
	Rat	Lichtenstein et al.[75]
	Rabbit	Chomette,[14] Brinsmade et al.[10]
	Mouse	Smithberg et al.[110]
Cortisone	Mouse	Fraser and Fainstat[29]
Vasopressin	Rat	Jost[62]
Adrenalin	Rat	Jost[61]
Alloxan diabetes	Mouse	Ross and Spector[100]

Insulin has been investigated as a teratogen in several species. Studies on this compound and others which acted in related fashion on the developing chick led Landauer[71] to emphasize the importance of carbohydrate metabolism in the early embryo. Of interest in this connection was the production of malformations in mice by alloxan-induced diabetes in the mother.

The teratogenic action of cortisone may also result from interference with carbohydrate metabolism. Fraser and his associates[29,30] have used this agent to demonstrate convincingly the dependence of the teratogenic action of an agent on the genotype of the subject animal. More will be said about this important point later.

Jost[61,62] has shown that adrenalin or vasopressin (Table V) can cause spontaneous amputations to occur in utero in rat fetuses. These are the direct result of hemorrhages in the extremities, but it is not certain whether the latter should be attributed to capillary fragility or to vasoconstrictive phenomena.

Miscellaneous Chemicals and Drugs.—Here is grouped a number of substances (Table VI) which fit into none of the preceding categories and which have little in common except that they have been used to produce malformations experimentally. Trypan blue is one of the most extensively studied of experimental agents, despite the fact that its teratogenic action was discovered only a little more than 10 years ago. From the first it appeared to be a promising substance for the study of the mechanism of chemical teratogenesis: (1) it is simple to administer, (2) it produces a high yield of defective offspring, and (3) it has numerous isomers, analogues, and otherwise closely related compounds. In the laboratory, however, its mechanism of action has proved quite elusive.

TABLE VI. MISCELLANEOUS DRUGS AND CHEMICALS THAT CAUSE MALFORMATIONS

AGENT	SPECIES	REFERENCE
Trypan blue	Rat	Gillman et al,[31] Wilson,[130] Fox and Goss,[27] Gunberg[44]
	Mouse	Waddington and Carter,[121] Murakami,[81] Hamburgh[48]
	Rabbit	Harm,[52] Ferm[24]
	Hamster	Ferm[25]
	Chick	Beaudoin and Wilson[7]
Vitamin A excess	Rat	Cohlan,[15] Giroud and Martinet[37]
Nicotinic acid excess	Chick	Hansborough[49]
Quinine	Chick	Ancel[4]
Antibiotics	Rat	Filippi and Mela[26]
Sulfanilimide	Chick	Ancel,[3] Landauer[71]
Chelating agents	Rat	Tuchmann-Duplessis and Mercier-Parot [120]
Colchicine	Chick	Paff[96]
Phenyl mercuric acetate	Mouse	Murakami et al.[83]
Thallium	Chick	Landauer[71]
Lead nitrate	Chick	Butt et al.[11]
Nicotine	Mouse	Nishimura and Nakai[93]
Salicylates	Rat	Warkany and Takacs[126]
Sugars	Chick	Hunt[56]
Eserine	Chick	Ancel,[3] Landauer[71]
Boric acid	Chick	Landauer[71]
Pilocarpine	Chick	Landauer[71]
Selenium salts	Chick	Franke et al.[28]

Only recently has the probable site of action, that is, whether in the mother, the placenta, or the embryo, been demonstrated. Beaudoin and Wilson[7] showed that the dye affects similarly the developing chick as well as the rat and mouse, thus tending to rule out the mother and placenta as sites of action. Ferm[24] has shown also that the dye is present within the blastocyst of the rabbit in appreciable quantity at about the time differentiation begins. More than 20 closely related azo dyes have been tested for teratogenicity in my laboratory, and only one, Evans blue, has shown any appreciable activity. Considering the similarity in chemical structure between the teratogenic and the nonteratogenic dyes, it must be concluded that whatever its mechanism, the action of trypan blue is remarkably specific.

It is noteworthy that an excess of two vitamins, vitamin A and nicotinic acid, can cause abnormal development of the embryo. It will be recalled that vitamin A deficiency also resulted in malformations, but, as might be expected, the types of defects caused by excess and deficiency are quite different. Dietary deficiency of nicotinic acid has not been found to be teratogenic, but specific antagonists of nicotinamide, a slightly altered metabolite of nicotinic acid, did cause maldevelopment.[72]

Salts of heavy metals have been found to be teratogenic in three instances. The remaining substances in Table VI are remarkable mostly for the varieties of chemical structure and physiologic activity which they represent.

Other Possible Approaches.—On theoretical grounds there are other categories of factors not included which would seem to be promising areas for investigation. Gluecksohn-Waelsch[38] has shown that maternal mice immunized against adult brain tissue gave birth to offspring, 8 per cent of which had malformations of the central nervous system. Further work on the possible roles of immune phenomena in teratogenesis certainly seem called for. Another area needing attention concerns the effects on the developing embryo of altered physiologic states in the mother. Such things as derangements of water and electrolyte balance, reduced liver function (particularly detoxification), and certain endocrine imbalances during pregnancy have been only sketchily studied, if at all.

FACTORS THAT FAILED TO CAUSE MALFORMATIONS

The factors listed in Table VII have been applied to the developing embryo without teratologic result. These probably represent only a small portion of those actually tested and found ineffective. Every teratologist has obtained only normal young when some of his best ideas were put to test. Pharmaceutical laboratories test many new drugs on incubating eggs and pregnant rodents but do not publish the negative observations. The items presented were selected from a much larger list, either because they were representative of a group of similar agents or because, in my judgment, they seemed to be likely prospects as teratogens. Included are physical factors, endocrine conditions, nutritional deficiencies, infections, etc., all categories in which teratogenic agents have been found.

It is clear, therefore, that not all agents, however unphysiologic they may appear, are able to cause maldevelopment. To interfere with embryonic development an agent, it would seem, must bear some specific relationship to the chemical or physical needs of the embryo. This relationship may be in the nature of a deficiency (dietary) or an excess (endocrine) of factors normally present, or it may involve the introduction of a totally foreign factor which is able to disrupt normal metabolic processes (antagonists, x-rays).

TABLE VII. SOME AGENTS THAT FAILED TO CAUSE MALFORMATIONS

AGENT	SPECIES	REFERENCE
Elevated temperatures	Rat	Chin-Yun Hsu,[13] Wilson[131]
Mumps virus	Chick	Hamburger and Habel[47]
Rickettsial (Typhus) infection	Rat	Giroud and Lefebvres[35]
Severe hemorrhagic anemia	Rat	Wilson[129]
Vitamin C deficiency	Guinea pig	Harmon and Gillum[53]
Vitamin K deficiency	Rat	Moore et al. [80]
Pyridoxine deficiency	Rat	Nelson and Evans[89]
Essential fatty acid deficiency	Rat	Martinet[76]
Amino acid deficiencies	Rat	Sims,[107] Albanese[2]
Choline deficiency	Mouse	Meader and Williams[77]
Biotin deficiency	Mouse	Giroud et al.[36]
Thyroidectomy	Rabbit	Krichesky[70]
Thyroid deficiency (uracil)	Rabbit	Krementz et al.[69]
Ergot alkaloids	Rat	Shelesnyak,[106] Sommer and Buchanan[111]
Methyl Cholanthrene	Rat	Jackson and Robson[59]
Copper	Chick	Butt et al.[11]

GENERAL PRINCIPLES OF EXPERIMENTAL TERATOLOGY

Let us now consider, not the individual teratogen nor even classes of them, but the whole array of agents collectively to see what generalizations and basic principles may be derived from the results. After careful deliberation, and no little vacillation, as many as five generalities emerge which seem to be applicable to most teratologic situations. It is certainly premature to formulate these as universal laws of teratology. They are presented here only as points of reference for thinking and planning and as hypotheses yet to be put to the final test.

1. *The susceptibility of an embryo depends upon the developmental stage at which an agent is applied.* Stockard[112] recognized this principle, and in his experiments on the sea minnow did much to substantiate it, but he made the error of assuming that the stage of the embryo at the time of treatment was the only factor that determined maldevelopment. It is now recognized that the degree of differentiation prevailing within a susceptible tissue is the real determinant in this connection. In mammalian embryos differentiation does not begin until several days after conception; in the birds it begins almost simultaneously with incubation, the undifferentiated stage being passed within the genital tract of the mother bird. It becomes apparent when for the first time certain cells begin to show structural differences which foreshadow their destiny to form particular organs and systems. There is general agreement that such structural changes

are preceded by several hours by changes in cellular chemistry, in other words, by chemical differentiation.

Malformations do not occur in mammals when a teratogenic agent is applied prior to differentiation. This has been clearly demonstrated by Russell[105] and by Wilson[128] with x-rays and by Nelson and associates[90] with dietary deficiencies. The only apparent exception was in an experiment involving hypothermia[109] in which one litter of abnormal hamsters occurred after treatment several days before differentation began. There is reason to believe, however, that this single instance could have been a "spontaneous" occurrence rather than one induced by the treatment. To explain the lack of malformations prior to differentiation it must be emphasized that all cells are structurally and chemically alike and accordingly would be expected to react alike. If the agent is potent enough to kill or severely damage the cells, all will tend to be affected alike and the embryo will die. If the agent inflicts only minor damage, the regulative powers of the embryo could be expected to restore the injured cells. Thus, specific defects cannot occur until groups of cells have differing susceptibilities and potentialities.

Teratogenic agents are most effective during the early stages of differentiation: smaller doses are required, a greater variety of defects is produced, and the defects are likely to be of a more serious nature. Each organ and system appears to have a *susceptible period* early in the differentiation of its primordia. Landauer[71] has shown that the height and duration of the susceptible period may vary with different agents. Russell[104] has demonstrated that the duration of the susceptible period can often be lengthened by increasing the dosage of the agent. The onset of the susceptible period varies somewhat from organ to organ,[134] but for most organs it falls within a few days of the earliest differentiation within the embryo, hence the over-all greater effectiveness of most agents at this time. An acute teratogenic stimulus, that is, one that is time-limited, produces a narrower syndrome of defects than when the same agent is allowed to act over a longer period.[90,134]

Susceptibility to teratogenic agents in general decreases as organ formation advances and usually becomes negligible after organ formation is substantially completed.[54,125,134] In fact, during the fetal period the only effect may be inhibited growth or, occasionally, pathologic degeneration.[54] As will be discussed below, some agents act differently at early and at late stages of differentiation.

2. *Each teratogenic agent acts in a specific way on a particular aspect of cellular metabolism.* Final substantiation for this principle will, of course, depend upon more extensive knowledge of the mechanisms of teratogenic action than is now available. Nevertheless, it is supported by existing information on mechanisms, which will be discussed later, and by several lines of indirect evidence. In the first place, every agent tends to produce a characteristic, though not necessarily unique, array or pattern of malformations when applied to a given species at a specified time (Table VIII). If the patterns produced by two agents acting at corresponding times are entirely different, it can be assumed that the agents act on entirely different phases of embryonic metabolism. An overlap in the patterns, that is, a duplication of one or more individual defects in the patterns

caused by two agents, can be regarded as due to the action of both agents on similar phases in the development of the defects common to both patterns. When the total patterns produced by two agents are the same, or very similar, close relatedness in the mechanisms of action is taken for granted.

TABLE VIII. PATTERNS OF CONGENITAL DEFECTS PRODUCED IN THE RAT BY DIFFERENT TERATOGENIC AGENTS*

AGENT	MOST FREQUENT DEFECTS	OTHER DEFECTS
Vitamin A deficiency	Coloboma of retina, ectopic ureters, diaphragmatic hernia	Hermaphroditic tendency, fused kidneys, postlental fibroplasia, various cardiovascular
Riboflavin deficiency†	Shortened long-bones and mandible, fused ribs and toes, cleft palate	Open interventricular septum, hydronephrosis, hydrocephalus, microphthalmia, hernias
Folic acid deficiency	"Universal teratogen"	Affected virtually every organ and system in body, varying considerably with time of treatment
Irradiation	Anophthalmia, encephalocele, etc., renal agenesis	Microphthalmia, various spinal cord, various cardiovascular, facial clefts, micromelia

*These were selected because the times of treatment and methods of studying the young were comparable. (See Tables I and II for appropriate references).

†Deficient diets alone produced mostly skeletal defects. Use of the antagonist galactoflavin caused, in addition to the skeletal defects, several visceral abnormalities.

These generalizations on the specificity of teratogenic agents are well borne out by the work of Landauer[71] on chemical teratogenesis. He compared the effects of six different agents applied to developing chicks on the fourth day of incubation (Table IX). Although all of the six agents acted primarily on the skeleton and produced many similar effects, definite qualitative as well as quantitative differences in the patterns were produced by all but the first two of these substances. The agents could be divided into two groups on the basis of whether their deleterious action could be prevented by the administration of nicotinamide. This strongly indicates that at least two basically different pathways of action were involved. Another piece of evidence supporting the specific chemical nature of teratogenic action was noted in connection with the fact that insulin causes different malformations if applied to the chick at different times in development. During an early susceptible stage, at which rumplessness is the characteristic defect, pyruvic acid was effectively used as a protective agent to prevent malformations. During a later susceptible stage insulin tends to cause micromelia and beak defects, but these were prevented by the administration of nicotinamide. Nicotinamide at the earlier period and pyruvic acid at the later period were of no protective value. Furthermore, although nicotinamide protected at the later period against both types of insulin-induced defects, namely, micromelia and beak defects, it was found that citric acid would protect against the beak defects

but not micromelia, and lactic acid against micromelia but not beak defects. The implication is clearly that a teratogenic agent can act on one or more specific metabolic pathways at one or more times in development, as evidenced by the fact that specific supplements can prevent the occurrence of single malformations or time-related groups of malformations.

TABLE IX. DEFECTS PRODUCED BY SIX DIFFERENT AGENTS IN CHICK EMBYROS 4 TO 5 DAYS OF AGE

AGENT	FACE	LEGS	TOES	OTHER
Sulfanilamide	Parrot beak	Bending of tibiotarsus	Syndactyly	Clubfoot
Eserine	Parrot beak	Bending of tibiotarsus	Syndactyly	Clubfoot
Thallium	Parrot beak	Bending of tibiotarsus and femur	No Effect	Microphthalmia
Insulin	Short upper beak	Shortness and bending of tibiotarsus	Syndactyly (very few)	Microphthalmia
Boric acid	Short lower beak and cleft palate	Shortness and bending of tarsometatarsus	Syndactyly, lack of fourth toe	Curled toe paralysis
Pilocarpine	Short lower beak and cleft palate	Shortness and bending of tarsometatarsus	Syndactyly, lack of first toe	Clubfoot

Modified from Landauer.[71]

To illustrate the probability that there is relatedness of biochemical mechnisms when the patterns of malformations are similar, it is again only necessary to turn to the work of Landauer.[71] He noted that malformations resulting from boric acid injection and maternal riboflavin deficiency closely resembled one another. When the livers of boric acid-treated embryos were analyzed, they were found to be grossly deficient in riboflavin, strongly indicating a common mechanism of action for the two agents. On the basis of such results it was suggested that the primary effect of the teratogenic substances was to temporarily block the supply of certain coenzymes. In this light, susceptible periods become times of critical need by a group of cells for a particular substance which, if not available, causes interruption or distortions in the growth schedule.

It has been repeatedly shown that the incidence of malformations following a given dose of a teratogen decreases as the embryo grows older. As already emphasized this is a reflection of the fact that most organs pass through their periods of greatest susceptibility relatively soon after cellular differentiation begins, but another factor also probably enters into this picture. It often has been observed that the agent exhibits greater specificity, that is, produces a narrower range of effects as the embryo increases in age.[5,54,125,134] The more differentiated the tissues of an embryo become, the more specific or individualized should become the metabolic needs of the cells. Thus, it appears that, while susceptibility diminishes with advancing embryonic age, specificity becomes more sharply defined.

3. *The genotype influences to a greater or lesser degree an animal's reaction to a teratogenic agent.* This does not mean that the laws of Mendelian genetics can be applied in experimental teratology. Usually only in subtle ways is the genotype of the experimental animal manifested in the incidence or pattern of defects caused by an extrinsic agent. One of the more obvious examples is that cited by Runner[102] or a strain of mice which regularly produced 2 per cent of offspring with abnormalities of the cranium and ribs without treatment, but which produced 22 per cent of the same defects when the pregnant mothers were starved for 24 hours. Landauer[73] noted that many of the malformations which were produced by insulin injection into the incubating chick egg also occurred at a very low rate in untreated eggs. Several of the same defects can also be produced by injecting trypan blue into incubating eggs,[7] but the patterns of defects caused by trypan blue differed both qualitatively and quantitatively from those caused by insulin. Each of these agents exhibited a considerable degree of specificity in the types of malformations produced, but each also bore a certain relationship to the defects that occur spontaneously in the chick. Numerous other instances are known in which a teratogenic agent appears to accentuate the incidence of a defect which occurs sporadically without any type of treatment.

Another demonstration of the importance of genotype is the often-reported fact that not only different species, but different strains and substrains, react somewhat differently to the same agent. Fraser and Fainstat[29] have observed this in several strains of mice treated during pregnancy with cortisone. Gunberg[45] has shown that three strains of laboratory rats (two of them actually substrains) reacted differently to trypan blue injected under standardized conditions. The differences were largely quantitative but sometimes were of surprising magnitude, for example, the incidence of exencephaly was 17, 50, and 97 per cent in the three groups.

Fraser and his colleagues[30] have stated the belief that a majority of congenital defects are caused by a combination of circumstances involving many genetic and many environmental factors. Kalter[63,64] has provided an example of such interaction. An appropriate dose of cortisone injected into pregnant mice caused cleft palate in 100 per cent of the offspring of strain A, but in only 19 per cent of the offspring of strain C57BL. When the two strains were crossed so that a C57 male bred with an A female, 43 per cent of the young had cleft palate, which is about what would be expected. However, when the cross was the reverse, that is, a C57 mother and an A father, the incidence dropped to only 4 per cent. It was evident that the probability of cleft palate after cortisone injection depended not only upon the genetic constitution of the embryo but also upon the uterine environment in which the embryo developed.

Although by no means all induced malformations can be shown to represent merely the exaggerated incidence of an otherwise infrequent spontaneously occurring one, there are growing numbers of supporters for the hypothesis that induced malformations take the form they do because of an underlying genetic instability. Landauer[72] states the case in these words: ". . . our evidence

leads us to conclude that sporadic defects as well as experimental phenocopies (induced defects which mimic hereditary ones) are the results of events through which ordinarily hidden weaknesses of developmental equilibria become manifest and that these weaknesses have a definite, if complex, genetic basis."

4. *An agent capable of causing malformations also causes an increase in embryonic mortality.* It is probable that death and abnormal development are simply different degrees of reaction to the same noxious agent. The percentages of mortality and of malformation have been observed to increase in roughly parallel fashion as dosage is increased, at least up to the LD_{50}.[90,128] Embryos are able to tolerate small doses of most agents without any permanent change, hence exhibiting a "margin of tolerance." Each embryo, however, has a threshold above which irreparable changes occur, resulting in either malformation or death. The range of dosage in which these changes occur, the *teratogenic zone*, is usually quite narrow and a slight increment in the dose will often result in total mortality. Just as the threshold for malformations rises with advancing embryonic age, so also does the threshold of mortality.

5. *A teratogenic agent need not be deleterious to the maternal organism.* This fact is vividly illustrated by the occurrence of subclinical cases of German measles during human pregnancy. The woman may be scarcely aware of any discomfort as the result of an infection which may, nevertheless, cause extensive maldevelopment of her child. This is not a unique situation; it occurs with some regularity in experimental teratology. Murphy[85] has shown that several of the anti-metabolites which cause malformations and death in rat embryos do not appreciably affect the mothers until the teratogenic dose is multiplied many times over. This is not surprising for the embryo has no storage depots of essential metabolites and, if the supply of these is only momentarily reduced, the rapid growth schedule could be sufficiently unbalanced to cause distortions in growth, in other words, malformations.

Enough has already been said to indicate the fallacy of the time-honored notion that the embryo lives as a favored parasite upon the mother, able to obtain scarce materials at her expense. In every instance of experimental dietary deficiency during pregnancy the mother fared better than did the embryo, although the mothers usually did display signs of acute deficiency.

There are only a few situations in which an agent was shown to be as deleterious to the mother as to the embryo. Murphy[85] found two antimetabolites for which the LD_{50} was approximately the same for the pregnant rat as for the litters. Wilson[129] noted that severe hemorrhagic anemia usually killed the mother rat before there was any appreciable effect on the embryos; if the mother survived the offspring were normal. It is well known that many women give birth to normal infants after suffering acute illnesses during the early stage of pregnancy when the embryo would be subject to maldevelopment. It appears, then, that there is no standard relationship between the reaction of the pregnant mother and the reaction of her embryo to extrinsic agents. In looking for the causes of congenital malformations in man, therefore, we must not limit the search to factors that act adversely upon the mother.

MECHANISMS OF TERATOGENIC ACTION

By mechanisms of action is meant the ways in which a teratogenic agent exerts its adverse influence on the embryo. Although teratologists generally are beginning to think a great deal about mechansims, and perhaps a little less about methods, our knowledge of the former is still very limited. To the passing references already made to mechanisms, the following should be added. In the case of irradiation the passage of the rays through watery solutions, such as is the living cell, results in the formation of free peroxide radicals. These radicals act selectively on the sulfhydryl groups of certain essential enzymes, destroying the enzymes and thereby destroying or crippling the cells. Metabolic antagonists act by virtue of their capacity to substitute for a normal metabolite at one stage in a sequence of reactions without being able to react like the normal metabolite at a later stage. Such an antagonist competes for a place in the cellular chemistry which it is unable to fill as far as the metabolic needs of the cell are concerned. An example is the substitution of the normal vitamin riboflavin by the closely related galactoflavin. A further type of mechanism is exhibited by the alkylating agents which act by alkylating certain radicals on the nucleoproteins in cell nuclei, causing particular damage to cells with high mitotic rates. Nitrogen mustard is typical of this group. Although few are understood, it nevertheless seems likely that there are several pathways through which a teratogenic agent may affect embryonic cells.

VOL. 10 1959

Regardless of how it is mediated, the ultimate effect is probably one or another of two things, either *cell death* or *alteration in the rate of cell growth.* In case of death of all cells of a particular type, the result would be a deficiency in the definitive tissue or organ concerned, with possible secondary effects on neighboring organs or tissues, due to the changed physical relationships. If only a portion of such cells were killed, a partial deficiency of tissue would result unless the regulative powers of the embryo were able to compensate for the lost cells.

Theoretically growth can be altered by temporarily stopping it, by slowing it, or by accelerating it; but it is largely a matter of speculation as to the role played by each in teratogenesis. A temporary stoppage or slowing of mitotic activity would have the same over-all effect as death of a portion of the cells in that the growth schedule of the tissue would be out of phase with that of adjacent tissues. An accelerated mitotic rate would also put a tissue or organ out of phase with the growth pattern of other structures in the region. Patten[97] has proposed, with some justification, that localized overgrowth may account for such malformations as spina bifida. Completely unrestrained growth would, of course, constitute congenital neoplasms, of which several varieties are well known.

Fig. 1 is presented as a schematic representation of the growing embryo and some of its relationships to its environment. The embryo may be regarded as an increasingly elaborate set of chemical reactions, all of which stem from the genes of the fertilized egg. By innumerable steps of enzymatically controlled syntheses, three major stages of differentiation are achieved: first chemical, then cellular and tissue, and finally organ and functional differentiation. At all stages nutrients, oxygen, and the other materials needed for synthesis must be available

from the environment. Ordinarily the maternal organism, which constitutes the immediate environment, provides these and also protects the embryo from deleterious physical and chemical influences. Occasionally, however, this is not the case and an essential metabolite is withheld, or an enzyme is poisoned, or a nucleoprotein is destroyed. The agent responsible is a *teratogen*, and except for gene mutations, and possibly vascular accidents within the embryo, such agents always come from the environment.

But teratogens can cause malformations only after differentiation has occurred, that is after there are cells with different developmental potentialities. Before this a teratogen may kill cells or alter their mitotic rate, but this would not matter in the teratologic sense because all cells are alike. Only after differentiation do the cells have specific roles in furture development. Destruction or damage then may cause deficiency or other aberration in the organs which these cells are destined to form.

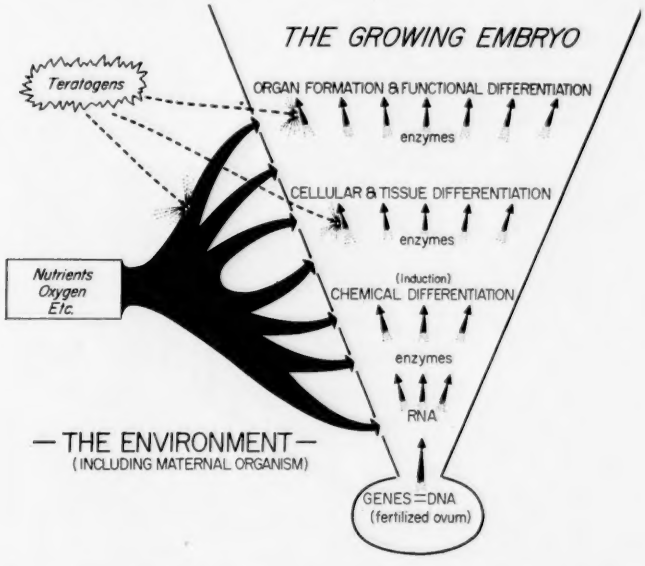

Fig. 1.—Schema illustrating the dependence upon the environment of the mammalian embryo at all levels of development for the materials needed in growth. Also occasionally coming from the environment are certain adverse influences called teratogens. These may be in the nature of an essential substance, such as a nutrient or oxygen that is withheld, or they may be substances which enter the embryo and interfere with chemical processes necessary for growth, such as would occur when x-rays or an antagonist destroys an essential enzyme. Teratogens are presumably able to produce specific malformations only if they act after differentiation has begun. Prior to that time an agent may also damage or destroy cells, but since all cells are alike all would be affected alike and the embryo would die or survive depending on the extent of cell damage.

SUMMARY

A survey of the literature reveals that there are approximately 60 methods whereby congenital malformations have been produced in laboratory animals. These were grouped into several categories as follows: physical agents, nutritional deficiencies, growth and metabolic inhibitors, infectious agents, endocrine states,

and a miscellaneous group of chemicals and drugs that had little in common except their teratogenicity. A representative list of agents that failed to cause malformations was also presented.

After careful consideration of the available information it was possible to formulate five general principles that seem to be applicable to most situations in experimental teratology. (1) The susceptibility of an embryo depends upon the developmental stage at which a teratogenic agent is applied. (2) Each teratogenic agent appears to act in a specific way on a particular aspect of cellular metabolism. (3) The genotype of the animal influences to a greater or lesser degree the reaction to a teratogenic agent. (4) Agents that cause malformations also cause a rise in embryonic mortality. (5) Teratogenic agents may have little or no deleterious action on the maternal organism.

Although present knowledge of the mechanisms of teratogenic action is meager, there are ample indications that several different pathways of action exist. Regardless of how it may be mediated, the ultimate action of all teratogens seems to be to produce either *cell death* or an *alteration in the rate of cell growth* (mitosis).

VOL. 10 195

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VOL.
10
1959

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SURGICAL TREATMENT OF BIRTH DEFECTS INVOLVING THE CENTRAL NERVOUS SYSTEM

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VOL. 10 1959

CONGENITAL, or what I prefer to call prenatal, defects involving the central nervous system and its coverings which are of interest from a therapeutic point of view include the following: (1) spina bifida and the various forms of meningocele and myelomeningocele, (2) cranium bifidum and the various forms of encephalocele, (3) congenital dermal sinuses, (4) diastematomyelia, (5) neurenteric cysts, (6) congenital types of hydrocephalus, (7) craniosynostosis, (8) arterial and arteriovenous malformations of the cerebral vessels, and (9) certain tumors derived from embryonic tissues, such as epidermoid and dermoid inclusion cysts, teratomas, craniopharyngiomas, and choroid plexus papillomas. All of these lesions are capable of producing crippling disorders of widely varying degrees of severity. All are capable of improvement or cure at some stage by surgical treatment.

Because the nervous system of the child is still growing and maturing, it is possible often to carry out prophylactic surgical procedures which, though not curative of an existing lesion, may be of great significance in arresting or slowing down a progressive disturbance of function. The results of preventive surgery of this type may be unimpressive at the time of execution or in the early postoperative course, but in the long run are extremely rewarding. Because of the importance of growth as a modifying influence on many of the congenital conditions mentioned, it may be necessary to continue careful observation as well as medical and various forms of surgical treatment over prolonged periods of time. Early recognition, definitive treatment, and faithful follow-up are all essential to optimum results.

These different categories of prenatal defects will be discussed in turn.

SPINA BIFIDA

Spina bifida is one of the commonest of all embryologic anomalies. Probably more than 20 per cent of all individuals will show some minor defect of a vertebral spine or lamina if survey roentgen-ray examinations are made. This anomaly

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represents a segmental abnormality of the invagination and separation of the neural ectoderm from the epithelial ectoderm, as well as a simultaneous abnormality in the development of the primitive mesoderm which gives rise to the bone and other supporting structures surrounding the neural tissue of the same segments.

From a surgical point of view, the lesions which are of importance include certain types of spina bifida occulta, spina bifida with meningocele, and some of the patients with spina bifida and myelomeningocele. Most patients with spina bifida occulta do not need any treatment and most infants born with total rachischisis are stillborn or survive only a very short period.

The presence of spina bifida occulta may be indicated by an overlying abnormal growth of hair, cutaneous angiomatous malformation, subcutaneous mass of fatty tissue, or dimpling of the skin. Children with any of these cutaneous defects should have roentgenograms of the spine made to establish the extent and type of the underlying spina bifida and should be watched carefully throughout growth for appearance or progression of any neurologic disturbance.

Spina bifida occulta may first be detected because of a neurologic deficit involving the lower extremities or control of the vesicle and rectal sphincters. Every infant or child who shows a congenital type of scoliosis, dislocation of the hips, pelvic asymmetry, positional deformity of the feet, absent deep tendon reflexes, or evidence of sensory impairment in the lower extremities should have careful roentgenograms made of the entire spine in search of congenital abnormalities. Occasionally, the primary complaint may be incontinence of urine, intractable bedwetting, or difficulty in bladder and bowel training.

One type of spina bifida occulta of particular interest is that in which a spicule of bone, arising from the posterior aspect of a vertebral body, protrudes through the spinal canal, dividing its contents into two separate compartments. This is known as diastematomyelia. Treatment consists of complete removal of the midline spicule of bone, lysis of adhesions from dura to the divided cord, and conversion of the double dural compartment into one space. The purpose is to remove any external distortion of the cord and to permit normal subsequent growth.

Surgical treatment in spina bifida occulta is generally limited to those patients who show evidence of a progressive neurologic disturbance as growth proceeds. This should be regarded usually as prophylactic rather than corrective surgery; its purpose is to allow further growth of the nervous system to proceed in as nearly a normal fashion as possible.

There is tremendous variation in the anatomic location, morphologic type, and clinical importance of meningoceles and myelomeningoceles associated with spina bifida. By far the commonest location is in the lumbosacral area. They may occasionally be multiple. Anterior meningoceles protruding into the thorax, abdomen, or pelvis rarely occur. In addition to the size, location, and covering of the meningocele itself, the most important clinical features pertain to the neurologic status of the segments caudal to the lesion and to the adequacy of cerebrospinal fluid circulation, that is, the presence of hydrocephalus.

VOL. 10 195

Abnormalities of spinal fluid circulation resulting in hydrocephalus constitute the most important complication to the management of infants with spina bifida. This hydrocephalus is due to malformation in the development of the hindbrain (Arnold-Chiari malformation). This anomaly consists of caudal displacement of the cerebellum through the foramen magnum, elongation, distortion, and caudal displacement of the medulla oblongata and fourth ventricle, and partial to total obliteration of the cisterna magna and surface subarachnoid pathways of the upper cervical spinal cord by dense adhesions.

There are few general rules which can be laid down for the surgical treatment of meningoceles and myelomeningoceles. Each patient's problem must be individualized. Ordinarily, simple meningoceles, without evidence of loss of neurologic function, should be repaired as soon as it is technically feasible. It is neither justifiable nor desirable to perform surgical procedures when it is clear that the infant is hopelessly and permanently crippled and that the chances of surviving to adult life in a useful fashion without encountering diastrous infection and gross retardation from progressive hydrocephalus are limited. If children with paraplegia survive on nonoperative treatment and appear to be developing normally, excision of a myelomeningocele may be indicated later in life as a means of facilitating nursing care and paraplegic ambulation.

In the presence of less than total paralysis associated with myelomeningocele, the lesion should be repaired at a time when the judgment and experience of the neurosurgeon indicate that the most favorable result can be achieved. It is essential before such repair is performed that hydrocephalus be absent, or controlled by surgery or spontaneous arrest. The leaking meningocele of the newborn infant should probably be repaired at once if any attempt at all is to be made to preserve life.

Home management, in lieu of, or awaiting, surgical treatment, consists of regular careful cleansing of the meningocele and the surrounding skin, protection of the sac against friction by a padded circular dressing, physiotherapy to the lower extremities, and regular observation for evidence of hydrocephalus.

The treatment of spina bifida is not finished with completion of a successful operation. It should be the surgeon's responsibility to see that head measurements are carried out for many months following operation to detect the possibility of delayed onset of hydrocephalus. It should also be his duty to see that orthopedic help is obtained to direct physiotherapy and rehabilitation of musculoskeletal abnormalities and to see that bladder and bowel training are pursued when these are indicated.

CRANIUM BIFIDUM

Fusion defects of the cranial vault occur much less frequently than do their spinal counterparts. By far the commonest location is in the occipital area where, in a high proportion of subjects, there is an associated intracranial malformation of nervous tissue or spinal fluid pathways resulting in some degree of hydrocephalus.

It is important that x-ray films of the skull be made whenever there is a midline protrusion of any kind on the scalp. If there is an underlying bony defect, the lesion should be considered as an encephalocele and operation should be carried out with preparations for dealing with intracranial structures should this be necessary.

Except in instances of obvious irreversible brain damage, where terminal care is imminent, surgical removal of encephaloceles is usually indicated in early life. The difficulties of feeding, handling, and ordinary nursing care with an encephalocele of any size are such and the psychic trauma to the parents in the presence of this disfiguring and unconcealable mass is so great that the earliest possible excision is highly desirable. Surgical treatment consists in amputation of the membranous sac followed by closure of the neck and firm approximation of the skin in two layers. If progressive hydrocephalus is present, this must be controlled before, or at the same time as, the encephalocele is excised.

VOL
10
195

CONGENITAL DERMAL SINUS

When the neural ectoderm fails to be pinched off completely from the epithelial ectoderm, a persistent tract or tube of stratified squamous epithelium may extend from the skin surface inward to the central nervous system. Such a congenital dermal sinus may occur at any point along the midline of the central neural axis. The most common locations are the lumbosacral junction and the region of the posterior occipital protuberance.

Such a sinus tract serves as a constant potential port of entry for infection. At any point along a congenital dermal sinus, and particularly at its innermost extent, there may be expansion of the sinus into a cystic mass. When such a mass occurs within the cranial vault or the spinal canal, it may act as any other expanding lesion to interrupt neurologic function by local compression of the brain or spinal cord, or it may cause interference with the normal circulation of cerebrospinal fluid. In the presence of unexplained meningitis in an infant, particularly if caused by *Staphylococcus aureus* or *Escherichia coli*, diligent search for a sinus tract opening should be carried out.

Surgical excision of the sinus tract should be carried out as soon as it is discovered. This should be done by a neurologic surgeon who is prepared to trace the tract into the central nervous system itself if necessary. The results of surgical treatment after abscess or meningitis has been established in patients with congenital dermal sinus are so poor that it is of the utmost importance to discover and remove these lesions prophylactically. Under the latter circumstances, the surgical treatment is simple and the prognosis excellent.

NEURENTERIC CYST

A rarer type of embryologic spinal defect is the neurenteric cyst, derived from both primitive ectodermal and entodermal layers. The cyst wall itself or a fibrous stalk from it may be intimately attached to the anterior surface of the spinal cord. There is usually a circular defect through one or more vertebral bodies, easily visible on x-ray films of the area, and there may be an overlying spina bifida occulta as well. The cyst itself is lined ordinarily by mucosa of ento-

dermal origin which may have the characteristic appearance of esophagus, stomach, intestine, or respiratory tract. Treatment consists of intraspinal removal of the cyst or stalk attached to the cord, followed if necessary by transthoracic excision of the extraspinal portion of the cyst wall.

HYDROCEPHALUS

Hydrocephalus refers to a pathologic condition characterized by an increase in the size of the ventricles and sometimes also part of the surface subarachnoid pathways as a result of the cerebrospinal fluid at some time being under increased pressure. Hydrocephalus is caused by the inability of cerebrospinal fluid to gain access to, or be transmitted across, the subarachnoid vascular barrier at a normal rate. Common sites of obstruction to spinal fluid flow include the foramen of Monro, lumen of the third ventricle, aqueduct of Sylvius, outlets of the fourth ventricle (foramina of Magendie and Luschka) and the basilar cisternae.

OL.
10
959

Among the types of hydrocephalus seen as a result of congenital anomalies are those associated with stenosis of the aqueduct of Sylvius, obstruction of the foramina of the fourth ventricle, and prenatal obliteration or failure to develop of the surface subarachnoid pathways, particularly those at the base of the brain. In addition, hydrocephalus frequently occurs in association with spina bifida and especially with lumbosacral myelomeningoceles. In these instances, the hydrocephalus is apparently always related to a congenital anomaly of hindbrain development which results in the so-called Arnold-Chiari malformation in which there is obliteration of the surface subarachnoid pathways around the brain stem and upper cervical spinal cord at the level of the foramen magnum. Hydrocephalus may rarely be due to congenital malformations of the cerebral vascular system also.

The symptoms and signs of hydrocephalus due to congenital anomalies are those of increased intracranial pressure. In slowly advancing hydrocephalus, there may be little in the way of symptomatology other than an accelerated rate of head growth. The diagnosis of hydrocephalus is confirmed and its type determined by a series of tests. Every hydrocephalic infant should be studied sufficiently to allow an authoritative decision to be reached regarding the indications for and type of treatment appropriate.

If there is reasonable evidence that there is still a chance for normal development, and it is established that progressive hydrocephalus is present, then the best available surgical procedure should be carried out as soon as possible. In the presence of gross irreversible central nervous system damage, which precludes a desirable result no matter how successful operative treatment may be, only custodial care should be recommended. Temporizing operations which permit infants who are blind, decerebrate, or otherwise irreversibly damaged to survive, but do not allow for normal brain growth, should be avoided.

The treatment of hydrocephalus is surgical. Until the past decade, the surgical treatment of hydrocephalus has been a record of occasional optimism and rare success but mostly of discouragement and failure. More recently, a variety of operative procedures in which spinal fluid has been shunted from one compartment of the spinal fluid pathway to another, or from the spinal fluid

pathway to some other location in the body where it could be reabsorbed or excreted from the body, have been employed with increasing success. Fluid has been shunted both from the ventricular system and from the surface subarachnoid pathways to a variety of distant locations, including the mastoid antrum, the pleural space, the peritoneal cavity, bone marrow, urinary tract, and the intrathoracic vascular channels. The shunting procedures which have given the most promise have been those into the peritoneal cavity, into the ureter, and by way of the internal jugular vein directly into the right atrium of the heart. In the latter procedure a competent valve must be placed in the shunt tube which permits only unidirectional flow from the lateral ventricle to the blood stream. Although far from perfect, diversion of cerebrospinal fluid through a catheter from an obstructed part of the subarachnoid pathway to some area of excretion or more adequate reabsorption appears to offer the best treatment of internal hydrocephalus available today. Many satisfactory results with normal mental and motor development for periods up to 10 years are now accumulating.

VOL
10
195

CRANIOSYNOSTOSIS

For reasons entirely unknown, but presumably as a result of a genetic defect in the germ plasm, the membranous bones of the skull, which normally are completely separated from one another at the time of birth, occasionally become fused prematurely. This condition, preferably called craniosynostosis, may involve any of the cranial sutures alone or in combination. In order for normal growth of the brain to be possible, the bones of the skull must remain ununited and capable of expansion. Therefore, if premature obliteration of the cranial sutures is present at birth, significant restriction of subsequent brain growth may occur.

Fusion of the sagittal suture alone is by far the most common variety. Coronal suture closure alone is the next most common, and following this, total synostosis of all the sutures is most frequent. Other single suture closure or combinations of various sutures are less frequently seen. The diagnosis should be suspected from the shape of the infant's head and can be confirmed by x-ray examination.

If the sagittal suture is closed at birth, the head expands abnormally in an anteroposterior axis and appears elongated and narrow. If the coronal suture is fused at birth there is abnormal lateral growth so that the skull appears wide, with a broad, flattened forehead. If the coronal suture is fused prematurely on only one side, this flattening is asymmetrical. When there is premature fusion of all the cranial sutures, growth is restricted in all directions and the head remains small with a tendency for it to expand upward in the direction of least resistance, that is, against the region of the anterior fontanelle.

There is a high incidence of mental retardation among patients with craniosynostosis, particularly when multiple sutures are involved, if surgical treatment is not performed in early life. It is of primary importance, therefore, to make the correct diagnosis and carry out surgical treatment as early as possible not only to minimize the cranial deformity but of greater importance to provide the best opportunity for optimum mental development.

In the first months of life, when surgery should be carried out if possible, the most physiologic type of treatment would appear to be creation of an artificial suture by linear craniectomy at the site of, or parallel to, the prematurely closed suture. The use of an inert substance such as polyethylene plastic film placed over the margins of the craniectomy openings has proved satisfactory in delaying the bony closure of these artificial sutures long enough to allow the brain to expand throughout the early period of rapid growth. It should be emphasized that this is prophylactic surgery in early life, and one should not wait for signs and symptoms of increased intracranial pressure to appear before carrying out craniectomy to open up prematurely closed sutures. There should be no mortality and no significant morbidity in performing the surgery indicated. Results are excellent when early surgery is properly performed.

OL.
10
959

VASCULAR MALFORMATIONS

Prenatal abnormalities of the intracranial vascular system include arteriovenous shunts of cortical vessels, arterial aneurysms, and cavernous hemangiomas. Disability in early life is caused particularly by the arteriovenous malformations in the form of intracranial hemorrhage, epilepsy, and retardation of mental and motor development. These lesions are localized by carotid and vertebral arteriography and their feeding vessels are defined. If favorably located, total removal can be carried out frequently. This type of surgery has been enhanced by the development of hypothermia and induced hypotension. Congenital sacular aneurysms of the circle of Willis, although rare, occasionally threaten life and health by rupture in early life. Their treatment in childhood by direct intracranial ligation has proved very rewarding. Intracranial cavernous hemangiomas may cause disability in early life as an expanding lesion or by spontaneous hemorrhage.

CONGENITAL TUMORS

For the sake of completion, certain prenatal neoplasms should be mentioned briefly. Benign congenital tumors involving the central nervous system produce disability because of compression of normal neural structures in their environment or by interruption of the circulation of spinal fluid. In the spinal canal, cystic epidermoid, dermoid, and teratoid lesions may cause paraplegia and be confused with such diseases as poliomyelitis, disseminated sclerosis, or inflammatory polyneuritis. These lesions have been seen most commonly in the cervical region and in the neighborhood of the conus medullaris. Subtotal removal with careful evacuation of cyst contents so as not to endanger normal neural tissue has been rewarded with significant and prolonged recovery.

Intracranial congenital tumors include, in addition to the dermoid and teratoid lesions, the craniopharyngiomas. These suprasellar tumors usually give rise to disability in childhood because of encroachment upon the optic pathways, the hypothalamus, the cerebrospinal fluid pathways, the pituitary gland, or any combination thereof. With modern steroid substitution therapy the results of surgical excision of these lesions have improved tremendously. This

type of surgery is most difficult and needs the support of competent metabolic and endocrine laboratories to be successful. Substitution therapy may need to be carried on indefinitely. Much is still to be learned about regulation of hypothalamic and hypopituitary states associated with these tumors.

Another intracranial tumor presumably of prenatal origin is the papilloma of the choroid plexus, a tumor which is circumscribed, does not metastasize, is capable of total excision, and is responsible for communicating hydrocephalus when it is present. This tumor has been recognized and removed successfully in the first few weeks of life.

SUMMARY

About 40 per cent of all admissions to the neurosurgical service of the Children's Medical Center, Boston, are patients with prenatal defects of the central nervous system or its coverings. The surgical treatment and total care of these children is often extremely complex and prolonged. Multiple operative procedures are frequently indicated. The results of such treatment are improving constantly. Fortunately, an increasing number of surgeons are interested in and capable of treating these lesions properly, because the number of children who can be benefited is great indeed.

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VOL
10
195

THE PROBLEM OF CONGENITAL MALFORMATIONS

General Consideration

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VOL.
10
959

THE excellent preceding presentations have dealt with prescribed and carefully limited aspects of the problem of congenital malformations. Each author has been able to probe more deeply in his particular area than I shall attempt. I should like to withdraw to a more distant viewpoint in a search for perspective, and shall discuss in quite general terms the answers to three basic questions: (1) How is a malformation defined and how is it identified? (2) How do malformations arise? (3) What effective preventive and therapeutic agencies are available?

DEFINITION

First, what is to be included in the concept, congenital malformations? The definition of a malformation would appear to be obvious, almost axiomatic, until one tries to formulate it. A structural deviation from the average norm, if it is rare and unfamiliar and therefore "unsightly," and if it is readily recognizable to the naked eye—like a cleft lip, or the presence of a sixth digit on one hand—patently constitutes a malformation. Concerning the grotesque and unusual there is no debate. But what of the acceptable and usual, the small pigmented mole, or the inconspicuous, pale, flat angioma or telangiectasis which most newborn infants show on the back of the neck or on the forehead and at the bridge of the nose and which tends to fade and disappear in the course of time? Or the so-called mongolian spots, hand-sized, well-demarcated areas of pigmented skin which can be found in about one out of eight newborn Caucasian infants, and somewhat more frequently among Negro children, spots which more often involve the buttocks than elsewhere and which also fade out and disappear within a few weeks or months after birth? Are any of these to be considered malformations in the sense which we are trying to define? Every serious investigative effort[7] to assess the frequency of congenital malformations in a representative population has at the outset come up against this formidable barrier to smooth progress, the fuzzy nature of the boundary lines of the items to be scored, requiring arbitrary and usually unsatisfactory drawing of cut-off lines separating, on an ad

hoc basis, what is to be regarded as abnormal and unexpected from the normal or expected. Up to now each study has had to write its own ground rules, since no body of arbiters has even been set up, much less gained universal acceptance. This is an important requisite which, it seems to me, ought to be supplied without delay. Proper study of the question of congenital malformations from a broad, epidemiologic point of view may be said to have barely commenced. If we are to learn the bases of pathogenesis, as we must indeed strive to do, then the problem must be viewed as a whole, not subdivided according to the rarity, or the lethality, or the supposed clinical significance of individual lesions. The majority of large-scale human studies of the past have been based on autopsy records, death certificates, and hospital charts, and thus include a limited segment of the total population involved. Conclusions based on biased observations of this sort must be interpreted with caution. Definition of scope therefore remains one of the cardinal requirements.

A second aspect of the problem of definition has to do with questions of structure and form. Shall we admit to the category of congenital malformations only those lesions which can be gauged with the naked eye, or is anything to be gained by including microscopic, even submicroscopic, deviations? For the serious investigator, the man from whom significant contributions to our knowledge are expected, much can be said in favor of including biochemical and metabolic anomalies along with structural malformations in a single research program. The statement has already been made that two general causes of malformation come into operation—genetic and environmental. Several clear examples are known of genetically transmitted anomalies, the most successfully documented of which are those which recur in each generation after the pattern of mendelian dominance. When a trait is transmitted genetically, it is passed from one generation to the next in the chromosomes, the nuclear material of the gamete. That which is so transmitted is not the supernumerary digit or the short digit but the gene for these anomalies, and virtually all geneticists now accept the evidence that the gene is itself a chemical substance, probably a particular form of desoxyribonucleic acid. The manner in which this substance, this gene, present in minute quantity (a fraction of the nuclear content of a single cell, perhaps only a single molecule of it enough to perform its task) produces the visible malformation in the course of growth and development of the embryo remains almost totally unknown, but the point can well be emphasized that genetic transmission of any characteristic, normal or abnormal, is mediated by a presumably unique chemical substance. The same mechanism serves for the genetic transformation of invisible as well as visible traits, of the various blood groups, of the sickle cell trait, of the capacity to taste certain substances, of left-handedness, of colorblindness, and so on through a spectrum of biochemical, metabolic, and structural abnormalities. Since these conditions or these diseases are believed to be alike in their mode of transmission and since they differ essentially only in their mode of expression, much is to be gained, presumably, from inclusion of metabolic anomalies among congenital malformations. Logically, by application of the same arguments, genetically transmitted traits which furnish the basis for a

much later appearance of symptoms and signs of disease, must also be included among congenital malformations, since they are in part responsible for such conditions as diabetes mellitus, Huntington's chorea, otosclerosis, migraine, and some of the forms of epilepsy.

A third aspect of the problem of definition has to do with the timing of the expression of a congenital malformation and the clinical aspects of its recognition. Those who have undertaken to measure incidence of malformations have been rightly troubled by the realization that a number of gross anomalies not visible on the body surface may not be recognized until they interfere with function to an extent sufficient to reveal themselves. Most of the malformations of the heart and great vessels produce some sign which leads to their early recognition. An infant with a malformation of the heart will have a murmur, a thrill, cyanosis, obvious cardiac enlargement, tachypnea, hepatomegaly, or some such manifestation so frequently as to lead one to assume that absence of all such clinical evidence of cardiac involvement completely exonerates this organ. Caution is necessary here too in interpretation of negative evidence. A bicuspid aortic or pulmonary valve does not give itself away by producing a murmur, but it is a malformation just the same. The fact that it may exist alone, unaccompanied by other more significant anomalies and unproductive of functional change, does not declassify it. Coarctation of the aorta and other malformations of the great vessels may be clinically silent until such time as growth of the infant or growth of adjacent structures brings to the fore some functional limitation. Many highly important, even potentially lethal, malformations of the urinary tract remain clinically silent until stasis brings on urinary infection, unless, as sometimes happens, they come to be discovered earlier through application of special diagnostic measures under the pressure of specific motivation. One of the most difficult assignments with which a pediatrician can be confronted is the assessment of an infant candidate for adoption when the foster parents ask that no stone be left unturned to reveal the existence of a malformation. Intravenous pyelography has perforce come to be an accepted component of the examination in these special circumstances. When no such drastic diagnostic steps are taken, how much goes unrecognized? One never knows.

Perhaps the most troublesome in this group of congenital malformations characterized by relatively late expression are those of the brain which lead to cerebral palsy or retarded intellectual development or to the all too common combination of the two. Despite continuing improvement in techniques of psychometric and neurologic assessment, despite increasing availability of diagnostic equipment such as electroencephalographs and maneuvers such as pneumoencephalography, and despite advances in the refinement and accuracy of interpretation, the fact remains that a considerable fraction of ultimately significant handicaps to intellectual growth and neurologic function remain undetected until the child reaches school age. These considerations, familiar to all pediatricians, militate against the possibility of ever attaining at any given moment of time or at any given age of infancy or childhood a completely accurate picture of the distribution and significance of congenital malformations.

PATHOGENESIS

The second area is that of pathogenesis—specifically, the pathogenesis of congenital malformations in man. Dr. Warkany has pointed out the lengths to which man's search for an explanation will go under the goading of imagination, and he has shown how impressive is the momentum of tradition, once a supposed cause of congenital malformations has been expressed and given credence through repetition with the voice of authority, regardless of its basis in fact. His review warns of the need to apply the utmost in skepticism, humility, and objectivity toward the collection and evaluation of evidence bearing upon this still mysterious problem.

Dr. Wilson has presented a skillfully condensed summary of experimental teratology, so far as its studies have been applied to mammals and birds. Since the entire methodology of the planned experiment has been marked "off limits" for the investigator in human teratology, not only in respect to experimental genetics but also in the control of the embryonic environment, there remain but two general methods of approach to the problem: that of reasoning by analogy with experiments carried out in the laboratory and that of the evaluation of experiments of nature. Each involves inherent limitations.

Dr. Wilson has been notably cautious in applying to man conclusions based on observations gleaned from experimental teratology. Indeed, one must recognize that the very breadth of his knowledge has counseled caution, for he has cited numerous examples in which a specific agent evokes a different response in one species as compared to another, often indeed in one strain as compared to another strain of the same species. After reviewing the entire field he has tentatively listed five generalizations which he believes apply to most teratologic situations (he carefully refrained from saying they apply to all). This means, I take it, that he has found these five generalizations applicable to all appropriate situations of experimental teratology and, at the same time, that he finds no conflicting or contrary evidence in human experience.

If the congenital malformations to which these generalizations apply are clearly identifiable as products of faulty embryogenesis, their pertinence is not open to question. In certain situations, however, it is difficult for the physician confronted with the living patient to know with certainty that the lesion identified has its basis in some error in formation of the fetus or in some later event. Two examples point up the difficulty. It is well recognized that in cases of cerebral palsy, with or without accompanying mental impairment, one cannot, with our present resources, be sure that the trouble arose, on the one hand, from faulty development of the brain during intrauterine life or, on the other hand, from some injury incurred at the time of birth; and this uncertainty often persists despite intensive clinical observation supplemented by postmortem study of the central nervous system. Generalizations pertinent to embryogenesis would have no bearing on a sequela of perinatal brain damage, despite its close resemblance in form and function to a developmental anomaly. As a second example I might cite the club foot problem. When a newborn infant is found to have any of the several forms of club foot, the clinician must try to ascertain whether the lesion

was genetically conditioned, whether it represents a developmental anomaly dating from an early period in the life of the embryo, or whether it was caused by retention during the final weeks of fetal life of a fixed position in utero. The three forms may look alike, but the first two have a quite different prognosis from the third and require a different schedule of treatment. Recognition of the third form of talipes, that dependent upon fixed intrauterine position which is by far the commonest of the three, is of relatively recent date and not yet universally attempted. Again the clinician's problem must be pointed out—the difficulty of distinguishing that which an embryologist might describe as a "true" malformation from a lesion which at first glance looks exactly like it but which follows an entirely different set of rules of play. The embryologist is of course right in asking the clinician to make this vital distinction in order to avoid errors of logic. The point to be emphasized is that, if we are to advance our knowledge of human teratology by applying to it concepts developed in the experimental laboratory, utmost care must be taken to avoid misinterpretation of the analogy through inadequate sorting of the evidence.

Close parallelism between results obtained in animal experiments and phenomena observed in human experience encourages one to apply the process of reasoning by analogy. Such a situation exists in regard to the analysis of injuries inflicted on the developing embryo by irradiation of the gravid uterus. Accidental radiation injury in man seems to be quite similar to that induced in a variety of mammals in planned experiments. Not only do the qualitative effects, the actual types of lesion produced, resemble each other fairly closely, especially in the apparently selective vulnerability of brain and eye, but quantitative factors likewise seem to operate in comparable ways. However, in other general areas, as in the study of the effects of infection, the behavior of experimental animals departs so widely from that of man that one wonders whether any gain whatever can result from reasoning by analogy.

The remaining weapon, observation of experiments of nature, has power when properly directed but is all too prone to bring down the wrong quarry. The instances which Dr. Warkany cited from medical history, of attribution of congenital malformations to machinations of Satan or to emotional crises experienced by the mother shortly before delivery, now appear to us absurd; yet they essentially reflected a strong drive to find an acceptable explanation for extraordinary events, a drive which persists equally strongly today but which must be channeled along other courses in order to find acceptance. So powerful is this urge to identify an acceptable explanation that even now the lay press is prone to grasp eagerly at any plausible hypothesis and to send it out for distribution in a form which the unwary easily accept as fact. As a group the medical profession has shown itself to be scarcely less gullible.

Some of the pitfalls which surround the interpretation of experiments of nature may well be briefly reviewed. Search for a causative mechanism usually begins with discovery of the malformation after the birth of the malformed infant. If a genetic component is to be evaluated, one must recognize that the average sibship is small, and that most parents can perhaps provide reliable information about their own parents but often little farther in the direct line of

forebears and even less about collaterals and about consanguinity in matings. Evaluation of the genetic component by observation of concordance or discordance in twin pairs seldom helps in the individual case; its application becomes a special study involving large scale surveys. Finally, the fact must be borne in mind that rigorous proof of the operation of a genetic component is seldom attainable in studies of congenital anomalies in man, whose matings from a statistical point of view have to be classified for the most part as random. Save for a few malformations which are transmitted by a dominant gene with a high degree of penetrance, such as brachydactyly and polydactyly, and which appear regularly in each generation, the most that can be expected is statistical support for the claim that genetic hypothesis satisfies the observed phenomena more closely than any alternative offered.

If the hypothesis of pathogenesis involves embryogenesis and the operation of factors of the uterine environment, retrospective analysis rests again on a shaky foundation. The circumstance that the significant events transpired in the past and must be recalled from memory in the absence of contemporaneous documentation involves a huge potential for the introduction of errors of fact. How can the investigator with a plausible hypothesis and a persuasive manner protect himself from the bias of suggesting to the mother or other informant the content of her recollections? In certain situations this source of error and uncertainty is removed, as when a mother has received therapeutic irradiation in a hospital or has been given drug treatment by injection so that dosage and timing are recorded with fair accuracy, or even when she has come under observation during a serious illness. However, when the environmental phenomenon under consideration is a modification of diet, a relatively insignificant and self-limited illness, consumption of a drug not requiring prescription, or any other comparably undramatic event, retrospective analysis forfeits all confidence. Probably the most one ought to expect of retrospective studies of pathogenesis of malformations is to confer some degree of plausibility on a hypothesis, with the expectation that a reliable judgment of causality must await the assembly of appropriate data from on-going or prospective observations, begun early in pregnancy and carried through to assessment of the offspring.

In the relatively brief period of years during which the capacity of rubella, incurred by a mother early in pregnancy, to cause conspicuous and serious malformations in the fetus has been recognized, a significant shift has taken place in the prevailing evaluation of the risk involved. For a time following Gregg's[3] first public announcement in 1941 of the increased incidence of cataract in the eyes of infants whose mothers had experienced rubella during pregnancy, the method of study was predominantly retrospective, beginning with the malformed infant and searching for a history or recollection of German measles at an earlier date. On the strength of these findings the risk of serious malformation was quite commonly held to be about 90 per cent if the mother contracted the disease during the first trimester of her pregnancy. On this basis hundreds, probably thousands, of pregnancies were interrupted under highly ethical auspices, a prophylactic trend which, if it achieved nothing else, surely served to becloud the unbiased observation of the natural course of events. During those first

years of evaluation of the rubella problem, while virtually every pediatrician of experience had personal knowledge of instances of malformed infants born to mothers who were said to have had rubella between 6 and 9 months prior to delivery, statisticians were acutely unhappy over the factual data which were being used as the basis of prediction of the risk. The first prospective studies, those which began with the observation of rubella during pregnancy and followed through to the ultimate assessment of the product of conception, suggested a far lower risk than 90 per cent; and yet as late as 1947[9] pooled reports were stressing ratios which implied an 86 per cent chance of serious trouble for the fetus if the mother's pregnancy was allowed to go through to term after she was known to have had early rubella. These contrasts are mentioned only to show how badly the public can be misled when in its desire for some sort of explanation it seeks satisfaction in hastily assembled data. With additional study the actual risk to the fetus, again assuming that the mother came down with rubella during her first trimester and then took no interfering action, has been calculated in various parts of the world—in New York,[2] Boston,[5] England,[1] and Sweden[6]—to be about 10 to 20 per cent, a very different degree of threat from the figure of 85 to 90 per cent preached earlier. This shift in emphasis raises a number of questions which may be pertinent to other studies of the influence of the uterine environment in the pathogenesis of malformations: Can one afford to pay more than passing attention to retrospective studies when the interval between the operation of the putative cause and the evaluation of the end result is as long as 6 months? Can we trust clinical and epidemiologic diagnosis of an environmental condition (in this instance, what has been taken to be a specific communicable infection) in the absence of some confirmatory laboratory test by which the specific etiology may be accurately recognized? How can rubella be defined, and can one be certain that the disease encountered in Australia in 1940 was the same as that which has formed the basis of subsequent studies made elsewhere? In the light of current knowledge, all of these questions must be answered in the negative or deferred for lack of information.

Considerations such as these may conceivably aid in the formulation of plans for future investigations. Studies of the rubella question constitute a prototype of inquiry into the effect of environmental agents. If infections are to be studied, and there is much to suggest that far more is to be learned in this area than we now know, identification of the infection and recording of its course, including its severity and complications, should have the benefit of all available supporting evidence and objective recording. Every other environmental component which is to be evaluated deserves the benefit of comparable objectivity. The strong probability that the great majority of pregnancies followed carefully in such an effort to document the experiments of nature will eventuate in normal growth and development of the fetus must be recognized from the outset and appropriate long-range plans must be made to see the project through to a valid conclusion. Firm evidence on the negative side, establishing the fact that the factor under study plays no part in determining the outcome of pregnancy, may have just as much value as more dramatic positive evidence and may in fact prove to be even more important.

One approach to the study of pathogenesis which has not been heavily exploited is the use of time schedules of embryonic development to identify the particular period during pregnancy when a teratogenic stimulus was applied. Irradiation, applied in heavy dosage at certain rather narrow time zones in the life of the fetus, affects growth of the brain and eye. The peak of the time curve of malformations produced by rubella falls in the second month following the last menstrual period,[8] and the common lesions produced involve the eye, the hearing organ, the heart, and the brain. These are examples of malformations the etiology of which seems reasonably certain, and the simultaneous injury of several tissues by a single pathogenetic factor seems fairly well established. But other malformations whose causes are still obscure show a comparable tendency to occur in clusters and to involve several different organ structures which might all have been undergoing rapid metamorphosis at the same time in the schedule of embryogenesis and which therefore might have been the more vulnerable to some environmental influence. Not knowing what influence to look for, we can tentatively offer as the next best course to determine the limits of the time zone during which such malformations could plausibly have been produced and search for factors out of the ordinary known to have been operative within that time zone. An example of malformation syndromes with several components is Turner's syndrome, which includes maldevelopment of the gonad, dwarfism, and frequently also coarctation of the aorta, cubitus valgus, and pterygium colli. Another is so-called congenital ectodermal dysplasia, in which the skin is devoid of sweat glands, the hair is sparse and slow-growing, the fingernails and toenails are malformed, and many of the dental follicles from which teeth are formed are totally lacking, while the few which are present give rise to misshapen teeth. The fact that this method of inquiry, focusing on the time schedule of embryogenesis, was applied with unconvincing success in an effort to clarify the pathogenesis of mongolism should not be permitted to discredit it as a tool of potential value.

The suspicion that the science of teratology is at the moment about to undergo a rapid expansion of our understanding of pathogenesis may be supported by citing two examples of relatively recent discovery in this general territory. The first and the better documented of the two is the demonstration that when a mother, in the effort to forestall a threatened miscarriage, is given certain progestin analogues during the early weeks of pregnancy her subsequently born daughter is apt to have conspicuous enlargement of the clitoris. The second refers to the assertion, recently made by two different laboratories in different parts of the world, that the chromosome pattern of mongoloid idiots is abnormal, showing an extra chromosome mass in one of the autosomal pairs of a large proportion of cells taken from bone marrow, and therefore presumably is discoverable, given adequate technical methods, in all the patient's cells. The latter observation may open a totally new avenue of approach to the problem of pathogenesis in congenital malformations of man.

TREATMENT AND PROPHYLAXIS

Many structural anomalies lend themselves to amelioration or even to actual correction through surgical intervention, and the number of lesions open to

operative approach appears to be increasing steadily. Dr. Matson has given us a concise summary of what surgery has to offer in coping with some of the malformations involving the central nervous system. Results are most satisfactory, it would seem, when the central nervous system itself is intact but is threatened by pressure from adjacent structures. The serious handicap under which surgery of malformations of the brain and spinal cord must labor is the inescapable fact that whenever, through anomalies of prenatal growth and development, important neural components are actually missing, their operative restoration is still utterly impossible and is likely to remain so despite advances of surgical science in other areas. Dr. Bronson Crothers used to refer to the valiant efforts of neurosurgeons in this connection as "mutilating operations." This is shocking language, and I am certain it was meant to be so; but those who knew Dr. Crothers understood that his objective was not to insult his colleagues of the knife and cautery but merely to startle them into an appreciation of the fact that surgery of the central nervous system, like all other branches of medicine, must recognize its limitations. The extraordinary progress that has been made within the last quarter-century in operative correction of congenital malformations of the alimentary tract, the heart and great vessels, and the kidneys and urinary tract must not be allowed to sustain the false hope that missing structures can be actually replaced.

OL.
10
959

Congenital failure of development of some major structures is incompatible with sustained postnatal life—anencephaly, for example, or congenital absence of both kidneys. Failure of development of certain glandular structures, however, often permits prolonged survival albeit under more or less conspicuous handicaps of growth and development. Congenital failure of the thyroid gland to develop leads to the familiar clinical entity, athyreotic cretinism; and in this virtually unique instance, if the condition is recognized early enough and if it happens not to be accompanied by other important malformations, particularly of the brain, replacement therapy by daily oral administration of an adequate dose of desiccated sheep's thyroid may restore the individual practically to normal. Although so favorable a result is admittedly unusual, the very fact that it can in certain instances be attained justifies a maximal effort not only in early recognition and treatment of congenital hypothyroidism but in comparable attempts to compensate for maldevelopment or nondevelopment of other endocrine glands. Some success has been achieved in treatment of so-called congenital diabetics—though whether this condition actually represents failure of development of islet tissue or collapse of islet function in response to some postnatal insult of unknown nature has not yet been established with certainty in any instance, so far as I am aware. Wilkins and his group[10] have had some success in substitution therapy of patients with congenital gonadal dysgenesis, particularly in causing cyclic menstrual bleeding in individuals with female genital and secondary sexual development but with male chromosomal configuration. Of course, such substitution could never be more than partial, affording some compensation for the missing endocrine component of the gonad but totally unable to stimulate the production of gametes. Substitution therapy in congenital absence of the parathyroids, or at any rate in congenital hypoparathyroidism, still lacks an

effective and reliable hormonal preparation and must strive for compensation through other devices for maintenance of physiologic concentrations of calcium and phosphate ions in the plasma. A comparable situation occurs in the recognition and therapy of congenital deficiency of the anterior hypophysis and of the various forms of congenital adrenal insufficiency, discussion of which would be out of place here. It should, however, be pointed out that the physiologic and biochemical means of early recognition of these subtle and recondite errors of development are constantly improving, that the armamentarium for effective substitution is constantly growing, and that this whole area is one which in these times lends itself to active and often fruitful exploitation.

Substitution therapy is not confined to congenital defects of endocrine glands but may at times be beneficial, even life-saving, in making up for congenital inadequacy or absence of various exocrine glands. I alluded previously to the syndrome of congenital ectodermal dysplasia. For more than 15 years I have had under observation a boy who was born without sweat glands, whose alveolar ridges contained but a single tooth bud instead of the normal thirty-two, and who had other anomalies of cosmetic but less vital concern. His first untoward symptom was fever—spikes of unexplained elevation of temperature, sometimes to 107° and even 108° F., unassociated with other signs of infection. With moderate elevations of temperature he would show little more than restlessness and apparent discomfort; but with the higher spikes, above 106° F., he appeared to be on the verge of convulsions. The usual studies were carried out in an intensive search for the infection which was assumed to be the basis of the infant's symptoms until someone noticed that his hospital temperature curve (this took place in summer) tended to rise during peaks of hot weather and to subside to normal levels in cool spells. It then became apparent that this infant could not dissipate heat by sweating and was very much at the mercy of the Manhattan climate. This suspicion was confirmed by closer observation of the dry state of his skin under conditions which caused everyone else in similar circumstances to sweat profusely, and finally by radiographic demonstration of the lone tooth bud —at an age when even a normal infant would not have had any teeth showing through the gums but when the x-ray could reveal calcified structures within the primitive dental follicles. The patient's fever was effectively dispelled by keeping him more lightly clothed and, during hot spells, by sponging his skin sufficiently to provide a wet surface for cooling by evaporation. The mother quickly caught on when shown what was required. During his second summer he spent the hot weather at a seashore resort and learned to supplement evaporation with immersion. He has had no unexplained febrile episodes since. Fitting dentures to the edentulous alveolar ridges of a growing boy constituted yet another aspect of his problem and involved the necessity of speech training. To make a long story short, his adjustment to his handicaps has been phenomenally successful.

Substitution therapy is part of the complicated battle in the management of patients with cystic fibrosis of the pancreas. Provision of pancreatic enzymes to take the place of those which are lacking as a consequence of the disease is not

difficult and sometimes makes for significant nutritional improvement, especially during infancy and early childhood. Supplementation of the mineral content of the diet with liberal addition of NaCl during hot weather and in anticipation of extra requirements resulting from violent physical exercise can successfully forestall episodes of circulatory collapse and so-called heat stroke and in certain circumstances may be life-saving. Extra food calories and vitamin supplements are required in proportion to the severity of the absorptive defect. Unfortunately this is about as far as substitution therapy goes in cystic fibrosis, for the physical properties of the altered mucus cannot as yet be modified by replacement therapy, and the pulmonary and bronchial infection must be combatted by altogether different means.

Many of the symptoms of cystic fibrosis seem to be dependent upon the physical properties of the mucus secreted in the alimentary and respiratory tracts. On the basis of recent studies these properties are associated with, and presumably determined by, peculiarities of chemical structure of the mucopolysaccharides, and these peculiarities may in turn be conceivably caused by absence of one or more of the enzymes which catalyze chemical reactions within the body. Enzyme defects, innate and persistent throughout the lifetime of the individual, make up an entire division of congenital anomalies in which new discoveries are constantly being made.

In general, the function of an enzyme in intermediary metabolism is to accelerate the conversion of one substance, which may be designated A and which constitutes the substrate of the reaction, to a second substance, B, which may be an end product or merely a single link in a metabolic chain. When the enzyme is absent or for some other reason fails to function, the first substance A accumulates in abnormal amounts and must be excreted or stored. Hereditary galactose disease[4] represents a good example of such a defect, in which absence of the enzymes galactose-1-phosphate uridyl transferase and galacto-waldenase causes galactose-1-phosphate to accumulate in the blood and tissue fluids following ingestion of lactose in milk. If the condition goes unrecognized for long, displacement of glucose by galactose so alters the composition of the plasma and other body fluids that alterations set in in nerve tissue with impairment of mental function, in liver with progressive cirrhosis, and in lens with the formation of cataracts. Removal of galactose from the diet enables the patient to replenish the glucose in body fluids as galactose, now no longer crowding in, is removed by excretion in the urine. Cataracts often resorb, liver function improves, and mental growth resumes. When galactosemia is recognized within the first month of life, before appreciable damage has been done to vital structures, the immediate institution of a milk-free diet provides complete protection against all of the injuries just mentioned, protection which appears to be lasting so long as the patient keeps to his dietary restriction. This is a gratifying measure of success, despite the fact that the enzyme defect is not repaired itself. Galactosemia is believed to be genetically transmitted, and the patient who has enjoyed the degree of protection described is supposedly capable of transmitting the trait to his offspring. However, insufficient time has thus far elapsed to permit any statement to be made concerning the fate of children of treated galactosemics.

Unfortunately, comparable examples of successful prophylaxis in congenital enzyme defects are rare despite the number and variety of such ills. Early detection of urinary excretion of phenylpyruvic acid by young infants led some years ago to efforts to prevent intellectual impairment—that is, to forestall the full picture of phenylpyruvic oligophrenia—by reducing or eliminating the substrate, phenylalanine, from the diet. Technically this is a far more difficult assignment than exclusion of galactose. If exclusion of phenylalanine is anywhere near complete, it is not only costly to an astronomic degree but it also deprives the patient of many normal gustatory pleasures. The modified diet, acceptable to a small infant, becomes progressively more distasteful to the subject as he matures. Further elaboration of the practical problems of prevention of injury in congenital enzyme defects is unnecessary beyond the general statement that the pediatric world is becoming progressively more concerned with the importance of early recognition of these metabolic anomalies, biochemists are alert to suggest ever new prophylactic devices, and in general the field of enzyme chemistry is currently being developed with remarkable rapidity.

Up to this point discussion of the treatment of congenital malformations has outlined some of its limitations and, in dealing with innate enzyme deficiencies, has gone over to the adjacent area of the treatment of the metabolic outcome, stressing the prevention of lasting damage while recognizing that for the present, at least, replacement of a missing enzyme is beyond the realm of possibility. Now it may well be asked, what do we know about prophylaxis of the congenital malformation itself?

The primitive state of our understanding of pathogenesis leaves little to be said about prevention. What knowledge we have of the genetics of specific malformations, enzyme defects, and so on serves the eugenics counsellor in calculating the odds that the product of a given couple's next pregnancy will or will not show the same defect that was recognized in an older sibling. To be sure, his advice must usually be hedged in several respects because of the ever-present uncertainty that a given trait will follow the classic course and because of his appreciation that, as Dr. Fraser pointed out, environment so frequently seems to influence expressivity of a gene. When once the participation of a genetic factor has been recognized in the offspring of a given couple, it becomes impossible to guarantee that the next child will be normal. At times the counsellor must recognize defeat and advise against another pregnancy. By and large, his lot is not a happy one.

The most practical aspect of prophylaxis I have left to the last. This has to do with the patient's own attitude toward his defect. To a very considerable extent the importance of a malformation must be gauged by the value which the patient himself assigns to it. Nothing helps a patient more than to be supported in the belief that his particular malformation is of no practical consequence. The lead in this legerdemain of persuasion has to be taken by the parents, by those who even while they outwardly belittle the significance of the anomaly stand ready to move heaven and earth to correct it. Difficult as it is to maintain such a double standard of values, the establishment of a constructive, forward-looking attitude within the home can prepare the patient, as he matures and as

VOL
10
195

his radius of experiences enlarges, to meet new contingencies with minimal awareness of the weight of his handicap. We have all seen examples of miserable failure, in which a patient has never been allowed for one instant to forget about his deformity. We have also seen brilliant examples of triumph. I suppose that every physician has his own model of success in coping with life despite a conspicuous malformation. History is full of such instances, famous men who overcame the handicap of a club foot or a deformed head to make their mark in the world of letters or art or science. The man I think of most often in this context is President Eliot of Harvard, who went through life with one half of his face marred by an undisguised, inescapable portwine stain. Not the least admirable aspect of his moral victory over his disability is the fact that his great contribution lay in the field of education. And not the least challenging of the considerations which arise when one is confronted with an infant or child with a congenital deformity is the thought that his full potential may bear little direct relation to the malformation present. In other words, what can be done, how can he be educated, so as to bring his potential to the fullest development of which it is capable?

In "Measure for Measure," Shakespeare puts these wise words into the mouth of Mariana:

> "They say, best men are moulded out of faults;
> And, for the most, become much more the better
> For being a little bad."

OL.
10
959

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THE REHABILITATION POTENTIAL OF PATIENTS IN CHRONIC DISEASE INSTITUTIONS

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VOL.
10
195

IT IS common knowledge that there are in nursing homes, county home infirmaries, and other long-term care facilities, a number of persons who would benefit from rehabilitation services if these were available. In order to study the extent of this problem and the nature of the presently unmet rehabilitation needs of these patients, a survey has recently been made under the direction of the Bureau of Chronic Diseases and Geriatrics of the New York State Department of Health.

In this survey, a cooperative clinical group of rehabilitation specialists visited nursing homes and county home infirmaries to evaluate the rehabilitation potential of a series of 1,480 patients. Their evaluations constitute the basis for this report. After considering as many factors as possible, the consultant physiatrists rated each patient's rehabilitation potential as either "definite," "slight," or "none." A physical profile developed by Dr. Eugene Moskowitz[6] was used to complement the diagnoses that were established. If any benefits were to be anticipated from rehabilitation services, the procedures recommended were stated, and a prognosis was established by setting forth a second profile indicating the gains that might be anticipated following the treatment that was recommended.

As a group these patients were elderly (median age, 77 years) and significantly disabled (2.4 major diagnoses per patient). The majority were recipients of public assistance. Approximately one-fourth of the group were in proprietary nursing homes and three-fourths were in county home infirmaries. Five counties in Upstate New York were represented in the study—Albany, Chemung, Erie, Onondaga, and Westchester; and 9 rehabilitation specialists† made the evaluations.

Shown in Table I are the over-all results of this survey. It is of interest that 15.1 per cent of the 1,480 patients evaluated were considered to have "definite" rehabilitation potential; and it was thought that 32.8 per cent might be

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benefited "slightly" from rehabilitation services; 52.1 per cent were considered incapable of rehabilitation.

TABLE I. OVER-ALL RESULTS OF THE REHABILITATION POTENTIAL SURVEY BY COUNTIES

COUNTY	REHABILITATION POTENTIAL			NUMBER OF PATIENTS
	DEFINITE	SLIGHT	NONE	
Albany*	25	41	57	123
Chemung*	9	3	1	13
Erie*	172	397	413	982
Onondaga†	13	24	192	229
Westchester†	4	21	108	133
Total	223	486	771	1,480
Per cent	15.1	32.8	52.1	100

*County home infirmaries only.
†Nursing homes only.

Further analysis of the data reveals two interesting observations: (1) a higher proportion of the men than of the women examined were considered to be candidates for rehabilitation services (Table II), and (2) the rehabilitation potential (synonymous with needs) of county home infirmary patients is appreciably greater than is that of nursing home patients (Table III).

Both of these observations can be largely explained by the factor of *age*. Whereas 75.4 per cent of the women were aged 70 years or over, only 66.1 per cent of the men were in this age group. Moreover, the nursing home patients were appreciably older (median age, 81 years) than the county home infirmary patients (median age, 75 years).

Indeed, age appears to be a very important factor in determining the extent to which patients can benefit from rehabilitation services (Table IV).

This by no means suggests futility in geriatric rehabilitation. It does indicate, however, that physiologic changes that accompany aging (such as diminished muscular strength and coordination) and pathologic factors (multiple disabilities) make successful rehabilitation more difficult for the aged. Translated into practical terms, it means that, for the aged, the rehabilitation goal is basically a lesser one than for younger persons. Seldom, for example, is vocational placement an objective for older patients.

Special mention is required for the small group of persons examined who were under the age of 40 years. Of the 19 patients in this group, all had extensive and frequently multiple disabilities. Advanced multiple sclerosis, postencephalitic Parkinsonism, and encephalomalacia following cerebral vascular accidents were the most frequent diagnoses. Only 2 of the group were considered to be candidates for intensive rehabilitation services.

The general types of disabilities encountered among the 1,480 patients in the survey are shown in Table V. The distribution of disabilities by organ

TABLE II. OVER-ALL RESULTS OF THE REHABILITATION POTENTIAL STUDY BY AGE AND SEX

AGE GROUP	REHABILITATION POTENTIAL											
	MALE				FEMALE				TOTAL			
	DEFINITE	SLIGHT	NONE	TOTAL	DEFINITE	SLIGHT	NONE	TOTAL	DEFINITE	SLIGHT	NONE	TOTAL
Under 40	1	3	2	6	1	6	6	13	2	9	8	19
40–49	5	7	6	18	7	5	3	15	12	12	9	33
50–59	29	31	28	88	7	22	8	37	36	53	36	125
60–69	59	72	54	185	13	33	38	84	72	105	92	269
70–79	54	124	136	314	25	60	96	181	79	184	232	495
80–89	8	55	151	214	12	51	161	224	20	106	312	438
90–99	2	10	34	46	0	6	42	48	2	16	76	94
100+	0	0	3	3	0	1	3	4	0	1	6	7
Total	158	302	414	874	65	184	357	606	223	486	771	1,480
Per cent	18.1	34.5	47.4	100.0	10.7	30.3	59.0	100.0	15.1	32.8	52.1	100.0

TABLE III. COMPARISON OF NURSING HOME PATIENTS WITH COUNTY HOME INFIRMARY PATIENTS WITH RESPECT TO REHABILITATION POTENTIAL

TYPE OF FACILITY	REHABILITATION POTENTIAL			NUMBER OF PATIENTS
	DEFINITE	SLIGHT	NONE	
Nursing homes	17 (4.7%)	45 (12.4%)	300 (82.9%)	362
County home infirmaries	206 (18.4%)	441 (39.4%)	471 (42.2%)	1,118
Total	223	486	771	1,480

TABLE IV. THE AGE FACTOR IN ASSESSMENT OF REHABILITATION POTENTIAL

AGE GROUP	REHABILITATION POTENTIAL						NUMBER OF PATIENTS
	DEFINITE		SLIGHT		NONE		
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	
Under 40	2	10.5	9	47.4	8	42.1	19
40–49	12	36.3	12	36.4	9	27.3	33
50–59	36	28.8	53	42.4	36	28.8	125
60–69	72	26.7	105	39.1	92	34.2	269
70–79	79	14.1	184	39.1	232	46.8	495
80–89	20	4.6	106	24.2	312	71.2	438
90–99	2	2.1	16	17.1	76	80.8	94
100 and over	0	0	1	14.2	6	85.8	7
Total	223	15.1	486	32.8	771	52.1	1,480

systems for the three prognostic categories shows no consistent pattern and suggests that the degree of disability, more than the type of disability, is the determining factor in limiting rehabilitation potential. It is interesting to note that the greatest number of disabilities per patient is highest among those whose rehabilitation potential was considered to be "slight." It seems probable that a number of these patients might have had "definite" possibilities for rehabilitation had it not been for the secondary disabilities that limited their capacity to improve.

Within categories, the diagnostic evaluations also were quite uniform. As one would expect, there were comparatively few patients with malignant diseases who were considered to have definite rehabilitation potential. It also is of interest that 42.8 per cent of the patients with musculoskeletal diseases (conditions with which one ordinarily expects improvement from medical rehabilitation) were considered to have no possibility of improvement. This, too, suggests that the extent of the disability is a prime factor in limiting a patient's potential for restoration.

TABLE V. MULTIPLICITY OF PATHOLOGIC CONDITIONS IN RELATION TO REHABILITATION POTENTIAL

TYPE OF DISABILITY	DEGREE OF REHABILITATION POTENTIAL						TOTAL	
	DEFINITE		SLIGHT		NONE			
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Nervous system	113	9.5	734	61.8	341	28.7	1,188	100
Special senses	12	6.9	107	61.9	54	31.2	173	100
Cardiovascular	133	11.9	674	60.3	310	27.8	1,117	100
Gastrointestinal	3	11.5	13	50.0	10	38.5	26	100
Respiratory	31	14.5	102	47.7	81	37.8	214	100
Musculoskeletal	75	11.3	306	45.9	285	42.8	666	100
Malignancy	6	6.7	58	64.4	26	28.9	90	100
Miscellaneous	8	13.3	22	36.7	30	50.0	60	100
Total	381		2,016		1,137		3,534	
Number of disabilities per patient	1.3		4.4		1.5			

The recommendations made by the examining physicians (Table VI) provide interesting information on services that presently are not available in most nursing homes and county home infirmaries.

TABLE VI. REHABILITATION PROCEDURES RECOMMENDED FOR PATIENTS EXAMINED IN THE REHABILITATION POTENTIAL SURVEY

RECOMMENDED PROCEDURE	NUMBER OF TIMES RECOMMENDED*	PER CENT OF TOTAL RECOMMENDATIONS
Recreational and/or occupational therapy†	401	29.0
Physical therapy	276	20.0
Ambulation training	214	15.4
Medical/surgical/dental treatment	181	13.1
Activities of daily living training	114	8.2
Braces or prostheses	52	3.7
Social service evaluation	37	2.7
Bowel or bladder training	35	2.5
Psychiatric assistance	28	2.0
Self-help devices	19	1.4
Speech therapy	14	1.1
Blind retraining	12	0.9
Total	1,383	100.0

*For 709 patients; number of recommendations per patient = 1.9.
†Includes sheltered workshop and part-time employment.

It is significant that the greatest single need is for services that give patients something to do. Physicians interested in geriatrics have long been impressed with the importance of keeping older people active, both physically and mentally, and this survey confirms their impressions.

DISCUSSION

Elderly persons and those who are chronically ill frequently require care of different kinds that vary from person to person and from time to time. Shown in Table VII are five levels of needs and the facilities that are appropriate for meeting these needs.

TABLE VII. FIVE LEVELS OF NEEDS AND APPROPRIATE FACILITIES FOR MEETING THESE NEEDS

NEED	APPROPRIATE FACILITY
Medical care	General hospital
"Intermediate" care	Chronic disease hospital
Nursing care	Nursing home
Personal care	Proprietary home for adults
Domiciliary care	Home for the aged

OL.
10
959

In Table VII there is indicated a dividing line between the need for medical, "intermediate," or nursing care, and the need for personal or domiciliary care. A person with one of the first three of these needs may properly be considered a "patient," whereas a person whose needs fall into one of the last two categories is not a "patient." It is suggested that the term "patient" be reserved for those who, in the event of an emergency such as a fire, would be unable to walk down a flight of stairs and out of danger without assistance.

There is little doubt that at present the need most difficult to meet is that for "intermediate" type of care, which for practical purposes can be equated with rehabilitative or restorative services. One can approach this problem in several ways: (1) by providing chronic disease hospitals with rehabilitation departments; (2) by constructing chronic disease wings as adjuncts to general hospitals; or (3) by encouraging nursing homes to provide extensive rehabilitation services.

The present study suggests the futility of the third of these alternatives. Nursing homes provide services uniquely appropriate for patients whose needs center around good nursing care, with a minimum of medical supervision. *But nursing homes are not, and should not be, rehabilitation centers.* Rehabilitation requires a variety of services (physical therapy, occupational therapy, speech therapy, activities of daily living training, etc.) that are most difficult for nursing homes to provide. *Nursing home patients with good rehabilitation potential have been improperly placed and should be transferred to other facilities better equipped to meet their needs.*

This does not mean that nursing homes should not provide limited restorative services. With proper orientation and training, the personnel of nursing homes can do much to bring restorative services (especially those that improve levels of self-care) to their patients. The present study suggests that approximately 15 per cent of nursing home patients in upstate New York would benefit from limited services of this kind.

Basically, the need in nursing homes is for more varied *activities*. Too frequently the remaining capabilities of older people are neglected and allowed to deteriorate. Patients in nursing homes should be encouraged to remain as active, physically and mentally, as their condition permits.

County homes are quite a different problem. These institutions provide domiciliary and personal care for those in need of such care. Often there is also an "infirmary" wing for the chronically ill and disabled. The level of care available in the county home infirmaries varies considerably, ranging from nursing care to medical care. This study suggests that nearly half of the patients in upstate New York infirmaries would benefit to some extent from rehabilitation services, and that in approximately 18 per cent of the total significant benefits would be derived were these services available.

Ferderber[2] in Pennsylvania and Dasco[1] and Tobis[8] in New York have pioneered in bringing rehabilitation to public home infirmaries. Their results are impressive and emphasize the importance of providing restorative services in institutions of this kind. In New York State, a number of county home infirmaries are currently developing rehabilitation units, now that the extent of the need for them has been delineated.

VOL
10
195

SUMMARY

1. In a survey of the rehabilitation potential of 1,480 patients in nursing homes and county home infirmaries, it was found that 15.1 per cent of those examined had definite possibilities of benefiting from rehabilitation; 32.8 per cent were thought capable of benefiting slightly from rehabilitation; and 52.1 per cent were considered unable to be rehabilitated.

2. Patients in county home infirmaries were found to have greater rehabilitation potential than patients in nursing homes and men more frequently were considered capable of rehabilitation than women. Both observations appear to be explained largely by the older age of nursing home patients and of the female patients in this study.

3. The extent of a disability appeared to be a more important factor limiting a patient's rehabilitation potential than did the organ system involved.

4. From this survey it is concluded that there is no pressing need for extensive rehabilitation services in nursing homes. Nursing homes are not and should not attempt to become major rehabilitation centers, although they can and should provide limited restorative services, chiefly those leading to improved self-care.

5. County home infirmaries have an appreciably higher proportion of patients in need of rehabilitation. Institutions of this kind should provide restorative services. The more difficult cases should be referred to specialized rehabilitation facilities.

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OL.
10
959

SOME COMMENTS ON "THE REHABILITATION POTENTIAL OF PATIENTS IN CHRONIC DISEASE INSTITUTIONS"

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VOL.
10
195

THE paper of Reynolds, Abramson, and Young entitled "The Rehabilitation Potential of Patients in Chronic Disease Institutions" is a useful one for it confirms statistically what has been generally accepted, that a significant number of patients in nursing homes would benefit from rehabilitative services. I find myself differing sharply, however, with the opinion expressed by the authors under the discussion primarily in two connections: (1) the introduction of a "chronic disease hospital," and (2) the conclusion that the nursing home is not a suitable place for rehabilitative services.

One of the steps we must take to get out of the morass of contradictory and poorly understood terms which have plagued the field of the care of the sick is to clearly define needs and clearly define facilities appropriate to those needs. It is high time that we give up the use of the term "chronic disease hospital." We should reserve the term "hospital" for that facility which provides definitive diagnosis and definitive care. If the "chronic disease hospital" provides definitive diagnosis and care it is and should be called a "general hospital." If it does not but provides lesser services, it should be called a "nursing home" or a "custodial institution"—a title appropriate to its function.

The conclusions that the authors draw about nursing homes being unsuitable for rehabilitative procedures is presumably based upon the unfortunate situation we find in the nursing homes in our communities. They are mostly proprietary. Their programs and facilities are generally poor. These facilities are not only unsuitable for rehabilitative services—they are unsuitable for any services. A modern nursing home under such auspices as to encourage good patient care, and intimately affiliated with a voluntary hospital, represents an ideal situation for rehabilitative services. Our view of a program of services and facilities designed to meet the needs of sick people envisions the modern general hospital at the center providing definitive diagnosis and definitive therapy. Once this active phase is over the patient then moves on to other facilities related to the hospital such as an outpatient department, if he is ambulatory; a home care program if his condition and home circumstances make this feasible; a custodial institution if the patient's disabilities require very long-term or permanent care; and a nursing home with care measured in weeks or months with the hope that the patient receiving intensive nursing services and rehabilitative services can be returned to communal living with or without further help.

Book Reviews

PLAYING FOR LIFE. By William F. Talbert with John Sharnik. Boston, 1959, Little, Brown & Company. Pp. 310. Price $4.00.

So you have diabetes. So what? It isn't a disease at all—just a biological fault! You need not concern yourself with what you eat or not eat, or whether your sugar is a fraction up or down. The main question is, how do you FEEL? What are you getting out of life? Would you like a dish of ice cream, a piece of pie, or a soda now and then? There is no ban against it.

> There is no longer any need, my doctor insists, to starve the diabetic, or to load his life down with food charts and elaborately regulated menus. A healthful diet, adequate for the activities of job, hobbies, household duties—this is the base. The right kind, amount and schedule of insulin will insure that the food is properly and beneficially used in the diabetic's system.

This book should be a source of hope to the million or more known diabetics in the United States. It makes good sense, yet it may be poor medicine for the "novice" diabetic. Many doctors would certainly be in disagreement with Mr. Talbert's philosophy, developed after years of experience with diabetes, and given indiscriminately to *all* diabetics. The diabetic must first *learn* the symptoms of the insulin reaction or diabetic coma before he knows why he feels as he does and what to do about it.

Mr. Talbert's story of his tennis career is unusually interesting. His experiences in making his bid for the top in tennisdom, which he reached, often tug at the reader's heartstrings. The behind-the-scenes social activities, which he thoroughly enjoys, are a revelation to the uninitiated-in-the-ways-of-big-time-tennis reader. His rise to the captaincy of the Davis Cup Team was a tribute to the great player and man that he is. His disappointment at being relieved of this post, but the good sportsmanship that he manifests, endear him to the reader.

Yes—diabetics need not be invalids.

Stanley J. Pawelek

VA PROSPECTUS: RESEARCH IN AGING. Veterans Administration, 1959. Pp. 125. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. Price $1.50.

I approached this little book with a cheerless heart. It looked like another symposium that should never have been recorded, let alone published. But the book is a pleasant surprise. Most of the presentations make stimulating reading, and a good bit of the discussion is also of interest. There is, of course, the usual unsuccessful series of attempts to define "aging," but I suppose the gerontologists have to be granted this recreation. (Don't ask me why.) The price is right, too.

Louis Lasagna

REHABILITATION CENTERS TODAY. A Report on the Operations of 77 Centers in the United States and Canada. By Henry Redkey. Rehabilitation Service Series No. 490, Office of Vocational Rehabilitation, U. S. Department of Health, Education, and Welfare, Washington, D. C., 1959, Government Printing Office. 231 pp., indexed. Price $1.00.

Many communities are eager to start rehabilitation centers or to improve inadequate facilities already in being. This detailed report has been collected by the Office of Vocational Rehabilitation to supply information on services, management, personnel, and costs of 77 centers in the United States and Canada.

The book is divided into three sections. Part One gives a general view of rehabilitation centers. It is a summary of types, costs, philosophy, and staffing needs of rehabilitation centers. In the second part, detailed information from the centers is reported, and in the final section, the 77 centers studied are listed with basic information about program, services, disabilities treated, and future plans.

The variability between different centers is remarkable. All centers have medical facilities, but some lack psychologic, social service, or vocational counseling services. Apparently anything from an outpatient physiotherapy department to an institution supplying elaborate services up to actual placement of the patient in a job may come under the heading of a rehabilitation center. This lack of uniformity among centers indicates the different ways in which community needs are being met. That existing facilities are in many cases inadequate is revealed by the fact that nearly every center reports plans for expansion, aimed toward making its services both larger and more comprehensive.

Douglas Carroll

THE YEAR BOOK OF DRUG THERAPY. Edited by Harry Beckman, M.D. Chicago, 1959, The Year Book Publishers, Inc. Pp. 569, indexed. Price $7.50.

THE YEAR BOOK OF MEDICINE. Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., W. B. Castle, M.D., T. R. Harrison, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. Chicago, 1958, The Year Book Publishers, Inc. Pp. 782, indexed. Price $7.50.

The new editions of these two annual volumes are in the tradition of their predecessors. They are well worth the purchase price as reviews of the past year's literature. Dr. Beckman's book is the more difficult to compile, since it attempts to cover the therapeutic waterfront and therefore encompasses more different kinds of journals than does the Medicine Yearbook. His task is also harder since he has to be critical and wise in more areas than any one man could hope to be expert in. One also has the feeling that the therapeutic "advances" recorded each year are more impermanent than the material covered by Beeson and associates. Yet the practicing physician at least ought to be aware of the new therapeutic claims, and the "consultant" will want to know the latest tricks to try in those cases not responding to usual measures.

The *Year Book of Medicine*, like the *Year Book of Drug Therapy*, is often best when it is recording the "asides" by its editors. These carefully phrased comments help tremendously to keep the abstracts in proper focus. In this category, Dr. Ingelfinger wins hands down. It is obvious that he writes his "editorials" with loving care, and this reviewer, at least, is duly appreciative. Here is a sample of Ingelfinger at work: "Some unhappy individuals become recluses because they cannot control the escape of noisy or odorous gas from a colostomy, but does not even the normal sphincter, Ogilvie's 'sentinel of social security' suffer similar mishaps?"

Ingelfinger for President.

Louis Lasagna